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subject of great practical importance and has been followed in this volume by two lectures dealing with basic knowledge on the subject, 'Experimental Hypothermia in Animals' by Audrey U. Smith and 'The Effects of Cold on Man' by O. G. Edholm. The importance for a healthy adult life of the environment in which the foetus is developed is becoming the object of study by modern methods and this field of research is represented by three lectures, by G. S. Dawes, J. Walker, and J. C. McClure Browne, the last of which discusses the use of radio-isotopes in the study of problems of pregnancy. The increasing usefulness of radiations in modern life and their possible destructive use in war require a better knowledge of the associated hazards, so that a valuable lecture in the present series is that by J. F. Loutit on 'Recovery from the Lethal Effects of Radiation'.

There are necessary limits to the use of the scientific method in the conditions associated with the treatment of human subjects and patients, and the clinician has had to depend largely on results obtained by the physiologist, biochemist, pharmacologist, and experimental pathologist for the scientific groundwork of his procedures. However, by adapting the methods of the laboratory to suit their special requirements, and by inventing new methods, clinical scientists in increasing numbers are carrying out controlled observations on human beings in health and disease, and themselves contributing to the scientific basis of medicine. Investigations of this kind are reported in the lectures by D. Slome on 'The Physiology of Nasal Circulation', A. C. Dornhorst on 'The Physiology of the Lower Oesophagus and Cardia', J. N. Hunt on 'The Investigation of Gastric Digestive Function in Man', M. D. Milne on 'Renal Control of Acid-Base Balance', and by J. F. Stokes on 'The Treatment of Hepatic Coma'.

The lecture by H. G. Davies on 'The Use of the Interference Microscope in Biological Research' illustrates the improved methods now available for the study and analysis of the very small by physical methods, and, in the opening lecture on 'Hypothesis and Speculation in Scientific Research', Sir Wilfrid le Gros Clark demonstrates the provisional nature of the conclusions of scientists in all ages and the need for scientific humility.

Volume VI of the series will be based on the lectures delivered during the winter of 1956–57 in which several of the subjects dealt with in this volume will be developed further. It will be published early in 1958.

FRANCIS R. FRASER
Director, British Postgraduate Medical Federation

9 January 1957

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NOTE

The lectures printed in this volume were delivered on the following dates:

I. 27 October 1955	XIV. 28 February 1956
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I

Hypothesis and Speculation in Scientific Research

SIR WILFRID LE GROS CLARK

When we look at diagrams illustrating the classical conceptions of Galenic physiology we may be tempted to regard them as the products of an imagination uncurbed by any reference at all to factual observation. But we should be very wrong to do so. The hypotheses advanced by Galen almost 1800 years ago, and accepted by anatomists for many years after him, were a serious and reasonable attempt to explain the working of the human body on the basis of direct observation. It was perfectly obvious to these early anatomists, for example, that something quite vital—an essential requisite for life—must pass down the trachea into the lungs, for any interruption of its flow would extinguish life very rapidly indeed. Clearly, also, this essence, or pneuma, must somehow enter the living substance of the body, and an obvious route for it to do so was evidently provided by the pulmonary veins along which it could be conducted to be infused into the blood at the very centre of life, the heart. It was also a matter of simple observation that the maintenance of vital activity depends on the ingestion of nutritive material in the food by way of the alimentary canal. And it appeared that the essence of this material could be conveyed from the intestinal tract (in the form of 'chyle') by way of the portal venous channels, and so to the liver. The inference that the liver elaborates the chyle into blood—in other words, that the liver is a blood-forming organ, was no doubt based on the observation that the fresh

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ADDITIONAL LECTURES

PHYSIOPATHOLOGICAL MECHANISM OF PAROXYSMAL ATTACKS OF ASTHMA AND THEIR TREATMENT WITH DRUGS

by

B. N. HALPERN

In this paper, we shall only consider attacks of true asthma such as those observed in young subjects. We shall not dwell on dyspnoea in cases of emphysema, broncho-sclerosis or right ventricular failure, the pathogenesis of which is of a markedly different type. A treatment, which is effective in true asthma, will fail and is often contra-indicated in other conditions marked by dyspnoea.

The difficult breathing of patients with asthma is mainly due to two causes: stricture of the respiratory tract and changes in the bronchial secretions. These two factors, which disturb the balance between the forces playing a part in the two phases of respiration to a different degree, afford a sufficient explanation of the mechanism of attacks of asthma.

1) Normal or eupnoeic respiration is a rhythmical, harmonious and unconscious succession of inspiratory and expiratory movements of equal duration, the frequency and depth of which are chiefly controlled by the respiration centre and modified by afferent nervous impulses propagated along the fibres of the pneumogastric nerve or arising from the reflexogenic areas of the aortic and cardic sinus.

The rhythmical discharges of the respiration centre are mainly dependent upon the CO_2 content of the alveolar air. The chief object of the respiratory movements is to maintain the composition of the alveolar air at a constant level.

Dyspnoea occurs as soon as the composition of the alveolar air has been disturbed. The changes in the composition of the alveolar gases appearing in asthma are due to obstruction of the air passages.

In normal respiration, the length of the expiratory phase is approximately equal to that of the inspiratory phase. Prolonged expiration is one of the chief characteristics of dyspnoea in cases of asthma. What is the cause of this particular feature?

Inspiration is effected by the rhythmical and periodic tetanization of the muscles of inspiration: diaphragma, muscles of the thorax, neck and abdomen.

Expiration is mainly ensured by the elasticity of the pulmonary tissue, which comes into play when the antagonistic action has ceased, i.e. when

the muscles of inspiration have attained the phase of hypotonia. Accordingly, the forces involved in ensuring the two phases of respiration differ markedly. Inspiration is effected with the aid of powerful muscles, readily able to overcome considerable obstacles, whereas expiration is only accomplished by the elasticity of the lung itself, a weak force, barely equivalent to a few centimetres of water pressure. An increased resistance in the air passages, which is only a slight obstruction to the act of inspiration, will more or less completely neutralize the force of expiration. Accordingly, the lung will be completely deflated when the next inspiratory phase sets in. The condition will be aggravated by the next respiratory cycle and this will rapidly result in overdistension of the alveoli As a result of the increased distension, the lung tissue accumulates a greater amount of elastic energy by which to expel the tidal air. Thus a new equilibrium of the air volume in the lungs is attained or the increased resistance due to the obstruction is counterbalanced by the increase in potential energy of an elastic tissue such as that of the lung. When the latter is kept in a state of prolonged excessive distension, the elasticity of the tissue tends to diminish as the duration and frequency of the attacks increase.

The slower movement of the air through the constricted bronchioles produces sibilant rales and rhonchi. This has two effects to which paroxysms of asthma owe their particular characteristics: an emphysema which is still physiological and reversible and a dyspnoea marked by prolonged and wheezing expiration.

Thus affords a rational explanation of emphysema with its well-known clinical and radiological features and of expiratory, wheezing dyspnoea, the two main symptoms of attacks of asthma.

In addition, there is a physiological phenomenon which causes aggravation. during the two phases of respiration the calibre of the bronchi is marked by variations that are the reserve of one another; during inspiration both the diameter of the bronchi and the length of the bronchial tree show an increase, whereas the calibre of the bronchi contracts during the expiratory phase The decrease in calibre of the bronchi during the expiratory phase acts as an additional resistance at the time when the air has to be expelled by the feeble action exerted by the elasticity of the lung and undoubtedly is an adverse factor. This effect, however, is compensated in normal conditions by the decrease in length of the bronchial tree. On the other hand, the rapid appearance of emphysema during attacks of asthma results in an excessive increase in length of the bronchial tree and thus neutralizes the favourable effect which normally counterbalances the decrease in diameter of the bronchi during the expiratory phase. The disturbances of the respiratory movements previously described also cause marked changes in the composition

of the alveolar air. The rapid onset of acute emphysema results in an increase of the dead space, not only owing to the excessive distension of the alveoli, but also as a result of the considerable lengthening of the bronchioles. The tidal air cannot effectively ventilate the alveolar air, which results in an accumulation of carbon dioxide, as shown by analysis of the respiratory gases and the appearance of cyanosis. The disturbances of pulmonary ventilation are obviously due to a decrease in calibre of the bronchioles. But is this caused by spasm or bronchial oedema?

As is known, the bronchial tree consists of a sheath of smooth muscle fibres, which increases in thickness as the bronchioles grow smaller. The longitudinally and circularly arranged muscle fibres interlace so as to form an intricately woven texture. The muscular sheath is made up of a padding of elastic tissue and lined with secreting ciliated epithelium.

The function of the bronchial tube is identical to that of the arterial tube. The structure of the bronchioles is such as to reduce the capacity of the respiratory tract to a minimum and to prevent dilatation of the subjacent structures, which are subjected to permanent stress caused by weight-bearing. The elastic tissue may give way, however, and collapse irreversibly under an excess of weight or as the result of prolonged action of a dilating force, giving rise to spherical distension of the alveoli.

These pressure-exerting forces to which the bronchial system is exposed are the act of respiration, coughing, etc , which tend to elongate and dilate the bronchioles and to cause spherical distension of the alveoli.

Being non-striated, the muscles of the bronchi also possess the other characteristics of smooth muscle fibres, i.e. they act independently. Even when they are no longer controlled by the nervous system, the bronchial muscles continue in a state of permanent contraction, upon which additional contraction waves are superimposed When stimulated locally, the bronchial muscles may respond by local or segmental contraction, even when they have been cut off from their nerve supply. This intrinsic myogenous action is controlled by the characteristic antagonistic double innervation of the autonomic nervous system

The fact should be borne in mind, that the bronchial muscles and glands are activated and stimulated by the cholinergic nerve fibres, whereas they are inhibited by the adrenergic fibres. When stimulated by acetylcholine and especially when stimulated by histamine, the bronchial muscles respond by contraction; likewise, administration of an antigen to a previously sensitized animal is followed by a violent bronchial spasm, which may be fatal. This bronchoconstrictive action of histamine and antigens may be neutralized by adrenaline or synthetic antihistaminics.

As stated previously, asthma is an allergic disease and one of the syndromes due to humoral allergy. By mechanisms, which we are beginning

to understand and in which injury, irritation and infection play the part of promoting factors, the antibodies in the blood are attached to the muscle cells of the bronchi, which then become the organs of shock. The reaction between the antigen and the antibody attached to the organ of shock gives rise to local liberation of histamine, resulting in obstruction of the bronchioles.

These facts are readily demonstrable in animals. When a guinea-pig, actively or passively sensitized to ovalbumin or heterologous serum, is made to inhale an antigen, it will die within a few minutes from asphyxia due to obstruction of the bronchi. When the bronchi of a sensitized animal are excised and suspended in a saline medium, in vitro addition of the antigen will induce violent contraction of the bronchial muscles. Studies by Schild and his associates have shown that similar or identical phenomena occur in human subjects: an asthmatic child sensitized to pollens and dust was treated with lobectomy for bronchiectasis in a London hospital. These English authors were able to obtain the resected specimen and dissected the bronchitic muscle, the reactions of which were studied in vitro. Addition of pollen or of an antigen consisting of an extract of dust to the solution in which the bronchus was kept alive invariably resulted in contraction of the bronchus. This contraction was of a specific character and could only be obtained by antigens to which the child had been sensitized. The contraction was inhibited by synthetic antihistaminics, but not by atropine. Accordingly, the results of experimental studies on animals and human subjects are similar in this respect: the reaction between the antigen and the antibody attached to the bronchial cell induces contraction of the latter as a result of the liberation of endogenous histamine. A more detailed study of the phenomena, however, shows that there is a marked difference between the mechanisms by which histamine and the antigen-antibody reaction induce obstruction of the bronchi, although the symptoms resulting in the animal's death from asphyxia are completely identical. When the animal has been poisoned by histamine, a bronchial spasm pure and simple is observed. On the other hand, the death of the animal treated with histamine aerosols is solely due to violent and irreversible contraction of the bronchioles.

The appearance of the bronchi of animals who have died during attacks of allergic asthma is markedly different. They are characterized by severe oedema of the areas of connective tissue and vessels surrounding the bronchi, which involves the muscles and mucosa.

This difference is readily explained: exogenic histamine, especially that administered by aerosols, chiefly causes a bronchial spasm, which results in asphyxia of the animal, associated with the symptoms of superacute emphysema, within a few minutes. The mechanism involved in attacks of asthma during the antigen-antibody reaction is more

complex: the endogenous histamine liberated by the endothelial cells of the bronchi causes vasodilatation and increased capillary permeability, resulting in oedema as stated previously, the obstruction of the bronchi in these cases being due partly to the oedema and partly to the spasm of the bronchioles.

Observations by M. Pasteur Vallery-Radot and Dubois de Montraynaud as well as personal studies have shown that oedema is an important factor in human allergic asthma. We have been able to induce attacks of asthma by inhalation of specific antigens in subjects affected with allergic asthma showing positive skin tests. Bronchoscopy, followed by biopsy, was done before, during and after the attacks of asthma. These clinical studies, which were as searching and accurate as a laboratory experiment, revealed the prominent part played by oedema, which came on with almost lightning suddenness and [illegible]

oedema observed in animals. But although oedema apparently is an important factor in the dyspnoea associated with attacks of asthma induced by allergens, we observed no definite signs of oedema in cases in which there was no evidence showing the asthma to be of allergic origin.

In that case, what causes dyspnoea in cases of asthma in which there is no oedema of the bronchi? The fact should be borne in mind, that the bronchi are characterized by an extremely vigorous contractility. Without dwelling on the peristaltic contractions, which no one has ever observed, the bronchi may respond to a variety of stimuli by the contraction of small portions, segments or regions. Mechanical stimulation is one of the most important types of stimuli capable of inducing contractions. Bronchoscopists are well acquainted with the spasm induced by the tip of the bronchoscope. The presence of a foreign body may give rise to segmental or regional spasms of the bronchi. Well then, apparently the bronchial secretions themselves, having undergone marked changes in asthma, may actually play the part of a foreign body in certain conditions. In addition to their obstructing action, which may be very slight, they may also cause a violent spasmodic contraction of the entire or of a larger or smaller portion of the bronchial tree by an axon reflex, like the action of an embolus on the vascular system. These contractions are not governed by the liberation of histamine, but controlled by the bronchomotor nervous system, which is supplied by the pneumogastric nerve. Therefore, antihistaminics will have no effect and a more or less complete arrest of the contractions can only be obtained by vagolytic agents, antispasmodics and sympathomimetic substances.

2) There remains the second problem: that of the rôle of internal secretions from the bronchi.

The secretions from the bronchi undergo marked changes in acute and chronic asthma. As is known, the bronchial tree is lined with a mucous membrane consisting of secreting as well as ciliated cells. The secretory system is composed of two types of cells: the goblet cells secreting mucin and the cells of the mucous and serous glands secreting mucus. The latter are controlled by the cholinergic nerve fibres; in addition, their secretions are increased by the substances which stimulate the parasympathetic nervous system, such as acetylcholine, pilocarpine, physostigmine, etc., and suppressed by belladonna and its alkaloids. The goblet cells are not controlled by the nervous system and respond only to local stimuli.

This being so, it is obvious that mucus plays a very important part in maintaining the harmony and equilibrium of bronchomotoricity. The mucus forms a homogeneous layer extending over the entire mucosa and thus protecting it against irritation by air-borne particles. It acts as a trap for bacteria, moulds and dust particles. The mucus, however, has another important function: it is essential to keep going the sweeping movement of the vibratile cilia. By their ceaseless sweeping movements, the latter are continually engaged in transporting secretions from the depth of the bronchioles towards the nasopharynx. The absence of a lining of mucosa in some part of the bronchial tree immediately results in an arrest of the sweeping movement of the cilia in this region, whereupon they promptly wilt and collapse. The ciliated cells in these regions are converted into goblet cells secreting mucin. When mucus is absent, the action of the cilia ceases and the secretions from the bronchi, thickened by the increased mucin content, tend to accumulate and stagnate. This stagnation promotes infection. Like foreign bodies, infected mucosities give rise to cough and cause segmental or partial spasms of the bronchial tree.

Normally, the cilia are able to displace 15 times the normal production of mucus. In that case, postural drainage does nothing to increase the effectiveness with which the bronchial secretions are eliminated. When, however, the cilia have ceased to perform their function, normal drainage will fail to remove the viscous bronchial secretions with their high mucin content. This results in a vicious circle: the damaged ciliated cells are transformed into goblet cells secreting mucin; the thickened and readily infected mucosities irritate the mucosa, which causes cough and segmental spasms giving rise to the sorrowful clinical picture of intrinsic asthma. When the irritation persists, the mucosa desquamates and is replaced by a lining of pavement epithelium, which has no useful function whatever. The bronchitic infections and cough subject the alveoli to

unusual degrees of over-pressure and, causing spherical distension, give rise to emphysema.

This physiopathological theory is based on sound observations and indisputable experimental data. They afford an entirely satisfactory explanation of the pathogenesis of attacks of asthma. Through the intermediary of the autonomic nervous system, mental factors may undoubtedly intensify the elemental motor and secretory reactions, but assuming asthma to be due to a particular mental condition would mean regarding as the cause what is merely the result.

Above all, asthma is an allergic disease, the mechanism of which may be explained by the fundamental concepts of the physiology of the respiratory tract and its disturbances during allergic sensitization.

The medical treatment of asthma is based on the physiological properties of the bronchial muscles and glands.

In the accompanying table, the various drugs acting on the bronchial muscle fibres and glands have been grouped according to their mechanism of action.

Cholinergic drugs stimulate the tonus of the fibres and the secretion of the bronchial glands, whereas the alkaloids of belladonna inhibit these two functions. This inhibitory action on the secretions frequently is a drawback.

Sympathomimetic substances mainly exert an effect on the tonus, without directly altering the secretions. The chief drawback to these substances is that they are habit-forming, so that the patient is compelled to take increasingly large doses, which results in status asthmaticus due to the use of drugs, unless precautions are taken.

The group of antispasmodics comprises substances that are very useful in treatment as well as agents the use of which is often fatal.

Theophylline and, to a lesser degree, caffeine, undoubtedly are the most valuable drugs for use in the treatment of asthma. I have no hesitation in stating that theophylline is the queen of antasthmatics. It may be administered by all routes and, more especially, parenterally and rectally. It is an only slightly toxic substance, acting on the smooth muscle fibres. Being a vasodilator, it promotes secretion from the bronchial glands. It is never habit-forming. Its cardiotonic effect and vasodilative action on the coronary vessels frequently are an advantage. Its slight stimulating effect on the mind, which gives rise to insomnia in certain subjects, may be readily corrected by administration of a small dose of barbiturate. Theophylline potentiates the bronchodilative action of ephedrine, which explains why combined treatment with these drugs is successful.

Morphine is classified with the group of drugs having an adverse effect.

Drugs acting on the bronchial muscle fibres and glands

	Preganglionic cholinergic *nerve fibres*	Postganglionic cholinergic *nerve fibres*	Adrenergic nerve fibres	Muscle fibres	Bronchial glands
Stimulating effects	*Acetylcholine and its esters*	*Acetylcholine and its esters*	Adrenaline	*Histamine*	Cholinergic drugs
	Physostigmine	Physostigmine	Aleudrine	K, Ba	Pilocarpine
	Prostigmin	Prostigmin	Tyramine		*Alkaline iodides*
	Nicotine	Pilocarpine	Ephedrine		Theophylline
		Muscarine	Benzedrine and its derivatives		
		Arecoline			
Depressant effects	Nicotine	Atropine	Ergotamine	*Theophylline*	Belladonna and its alkaloids
	Large doses of acetylcholine	Scopolamine	Dehydro-ergotamine	Morphine	
				Caffeine	Morphine
	Physostigmine (by preventing destruction of the liberated acetylcholine)	Hyoscyamine	Dibenamine	Papaverine	
				Antihistaminics	Antihistaminics
		Homatropine	Dioxane derivatives		

This alkaloid, which undoubtedly is the most marvellous drug furnished by nature, has been the cause of a large number of deaths in patients with asthma. The physician, who has been called in by a patient whose anxiety has often reached the culminating point, is inclined to pounce upon morphine to afford the patient some relief. There is no doubt that his anxiety will rapidly subside, but a few hours later the clinical picture is aggravated, dyspnoea recurs, cyanosis appears and the patient dies within 24—48 hours in a semi-comatose condition, literally drowned in his bronchial secretions.

This is due to the fact that morphine has both a depressant action on the respiration centre and a paralysing effect on the bronchi and suppresses the secretion from the serous glands essential to liquefaction of the mucosities thickened by the mucus.

, Papaverine has hardly any effect on the bronchi, in contrast with its powerful action on other smooth muscles.

A final remark on substances stimulating secretion. The other side to the picture of cholinergic substances, which stimulate secretion, is that they have a constrictive action on the bronchi. Only iodides and ipecacuanha are devoid of these effects. To-day they still are the most widely used liquefacient drugs.

DISCUSSION

NICOTINIC ACID AND ITS DERIVATES IN THE THERAPY OF BRONCHIAL ASTHMA*

by

LINO BUSINCO

In the guinea pig the single anaphylactic shock causes in the respiratory apparatus the characteristic picture of bronchial spasm and of a very extensive emphysema. On the contrary, repeated anaphylactic shocks that occur at a few days distance the one from the other, cause very deep alterations with a perturbation of the vascular system and especially of the capillaries (spasm or dilatation, edema of the large blood vessels, dilatation of the capillaries, eosinophilia and alveolar edema). There exists here a very remarkable capillary stasis which is accompanied by an increase of permeability and a transudation of plasma into the alveola. Bronchial spasm and edema of mucous membranes are equally observed, but the edematic-congestive suffering of the circulatory system and above all of the capillaries of the alveola is the dominant event. The allergen sensibilizes therefore all parts of the respiratory apparatus and even the capillaries, which are disturbed above all in their permeability. A direct consequence is the passage of capillary plasma into the alveola. There results then a dangerous reduction of the respiratory surface, a reduction of oxygenation, and [illegible] ob[illegible] bronchial asthma and above in the humid type with hypersecretion, and so on. With the purpose to make use in bronchial asthma of a therapy which may act in the same on the respiratory and on the cardio-vascular elements, we have turned our attention to nicotinic acid and to its derivates (amide and diethylamide).

Nicotinic acid presents the advantage to possess jointly the anti-allergic property and the cardio-vascular stimulant property, together with an elective action on the capillaries of which it protects the integrity. The anti-histaminic and anti-allergic action demonstrated by us since 1940 develops as well in the isolated organs, as in the experimental allergic inflammations and in the various allergic syndromes The therapeutic properties on the cardio-vascular system of the derivates of nicotinic acid are very well known

In the practic use we have employed above all the amide and the diethylamide of the nicotinic acid. The amide has been administered by injections in growing doses, from 0,1 to 0,3 or more, for the duration of a month. During the same time we have administered the diethylamide of nicotinic acid (coramin) orally, in the doses of 20 to 30 drops at a time; 3—4 times a day. With this therapy wr have the possibility to act upon the allergic factor as well as on the cardio-vasculae

* From the Institute of Medical Semeiology, University of Rome.

and particularly on the capillary factor. The clinical results are favourable in a good number of cases. The absolute harmlessness of this therapy permits us to recommend it, after a long experience, as well worthy of a more extensive practical use.

PROBLEMS CONCERNING THE PHYSIOPATHOLOGY OF BRONCHIAL ASTHMA

by

HELGE COLLDAHL

In severe asthma the pulmonary ventilation and oxygen uptake are not commen- [illegible]

[illegible] uptake of oxygen are lower than under basal conditions. This leads to the development of an oxygen debt during attacks, a deficit that must be made good afterwards. In mild asthma the pulmonary ventilation and oxygen uptake rise above the normal. No oxygen debt occurs.

The asthmatic breathing, as such, affects the body temperature. Severe and long-standing asthma leads to a fall of body temperature while mild persistent asthmatic breathing produces a rise. An elevated body temperature cannot, therefore, always be interpreted as a sign of a complicating infection

The systolic as well as the diastolic blood pressure, though the latter not so frequently, considerably increase as a rule during severe attacks in man. An elevated blood pressure together with severe asthma symptoms therefore do not with certainty indicate a state of primary hypertensive disease.

The altered gaseous tension during asthmatic attacks provokes changes in tissue respiration in animal experiments, partly caused by destruction of cozymase. The changed tissue respiration is caused by respiratory insufficiency and is not the result of [illegible]

[illegible]

During asthmatic attacks the pulmonary mixing capacity of the respiratory gases in the alveolar bronchial system decreases when studied by continuously recording the nitrogen elimination from the lungs during oxygen breathing The elimination of gases from the blood in the exhaled air is also diminished in asthma, as is shown by a new test of pulmonary and cardiovascular function, the P.A E.C. test The two lastmentioned tests do not run parallel with each other. When there is no stenotic breathing the washing out time for nitrogen is about normal, but even then the pulmonary acetylene elimination after intravenous injection of saline saturated with acetylene [illegible]

[illegible]

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J. F. FARRERONS-CÓ

The only point I wish to make in this discussion is the extremely important fact that the adrenergic system participates in the mechanism of the allergic reaction.

The following two slides will show you the results of my experiments with dogs. I determined the nor-adrenaline content of the dogs' blood before and during the anaphylectic shock It will be seen that the nor-adrenaline content increases in all cases This means that anaphylectic shock is not only a problem connected with the cholinergic system but with the adrenergic system as well

W. J. QUARLES VAN UFFORD

To show my great interest in the paper delivered by Dr Halpern, I also wish to [illegible]

It is given to prevent and treat acute attacks:

1) as an adjunct in the treatment of dyspnoea due to exercise (e.g 1 suppository of 360 – 480 mgm twice daily, or three times one powder or tablet of 200 mgm, often combined with administration of vitamin C),

2) as an adjunct in cases showing ECG changes;

3) as an adjunct in chronic shortness of breath associated with coughing, dyspnoea, etc. In these cases we prefer giving Ringer's solution or glucose by intravenous drip, daily for 10 – 12 hours, with 240 – 480 mgm. of aminophylline, combined with the administration of expectorants, antibiotics, etc. The patient often returns home at night, so that he stays in his usual surroundings as much as possible. In recent years this treatment resulted in the disappearance of the symptoms in fifty patients, who thus were helped to find a way out of the deadlock;

4) as an adjunct [illegible] giving aminophylline by intravenous drip (240 – 480 mgm. every 12 hours), if need be, several days in succession. This method has the additional advantage that, should the result be unsatisfactory, ACTH may be added to the

intravenous drip without the patient's perceiving any radical change in treatment. The main reasons for stressing this method of treatment have been the results obtained with intravenous drip in chronic shortness of breath, dyspnoea due to exercise and status asthmaticus.

F. WYSS-CERUTTI

[illegible]

being affected by a valvelike oclusion of the bronchiolar wall during expiration. Against this view Winthrich pointed out that asthmatic dyspnea was consecutiv to a cramp of the inspiratory muscles.

In the last 10 years we have investigated the different factors involved in bronchial asthma in order to elucidate this problems.

First of all it was necessary to calculate the degree of bronchiolar obstruction by measuring the resistance to air flow in the bronchial system. This can be computed from figures on the flow rate and alveolar pressure, which are easily available by applying the method of Vuilleumier, which I will not describe in this discussion.

The quotient of alveolar pressure and air-flow rate amounts in normals from 10 to 30 and in asthmatics from 30 to even over 100. During quiet breathing the flow resistance remains nearly constant during expiration, whereas forced expiration evokes increased bronchial resistance even in normals. In severe asthma forced expiration may lead to complete oclusion of the whole bronchiolar tree Even though intrathoracic pressure may reach 2500 millimeters of water under these circumstances no air is able to leave the lungs and the bronchiolar resistance therefore raises to infinite values. The valve-like mechanism can easily be explained by the following slide A great intrathoracic pressure is necessary in order to overcome the increased bronchiolar resistance. This intrathoracic pressure compresses not only the alveoles but as well bronchioles and the pars membranacea of the trachea and great bronchi. The collapsus of the pars membranacea which follows from this compression may very well be put to evidence by bronchoscopy.

Thus the bronchiolar stenosis and the exspiratory collapsus of the bronchial wall play a considerable part in the pathogenesis of asthma.

Now what about the inspiratory cramp of the respiratory muscles?

The fact, that the diaphragma during a severe attack of asthma may often be found in completely fixed inspiratory position and numerous other observations make a spasm of the inspiratory muscles very probable. The existence of such a mechanism could be proved through electromyographic studies. The derivation of action-potentials of the diaphragme is difficult and rather dangerous. We have therefore in our studies concentrated on the easily accessible sterno-cleido mastoideus and scalenus anterior. Eight healthy control-persons showed a more or less marked electrical activity during inspiration and not at all during expiration.

Asthmatic and emphysematic patients are however characterised by a very strong electrical activity during both parts of the respiratory circle. Occasionaly it may be seen that interruption of an acute attack by a bronchospasmolytic agent is followed by a prompt decrease or cessation of the spasm.

It is our opinion that the spastic activity of the diaphragma and of the other inspiratory muscles is induced by stretch receptores in the bronchial wall, which are connected by vagal fibres to the respiratory center. Time is too short to explain this probable mechanism.

It may be therefore that Biermer was as right as Winthrich, both the bronchiolar spasm and the cramp of the inspiratory muscles taking part in the pathogenesis of the asthmatic dyspnoea.

FURTHER OBSERVATIONS ON THE EFFECT OF SPECIFIC HYPOSENSITIZATION IN ASTHMA *

by

EGON BRUUN

Bray once said: 'The capriciousness of asthma is one of the most fascinating, even at the same time disturbing, factors in the study of the subject.' Probably, most of you will agree that also the *diagnostic problems* in asthma are both fascinating and worrying questions, and I feel convinced that you all share my feelings about the *treatment* of asthma which is at the same time a fascinating and wonderful inspiration, and on the other hand so capricious a task that it may bring you to the point of a nervous depression.

When, in a capricious disease, one is working with both capricious diagnostic procedures and capricious forms of therapy, the evaluation of the therapeutical results must be a somewhat delicate affair. To-day, the Committee has wanted an evaluation of one of the various forms of treatment of asthma, the specific hyposensitization, but it must be stressed at once, that specific hyposensitization is not the only form for treatment of asthma, and in some cases not even the best one. However, on the basis of more than 14 years' experience, I daresay that a specific hyposensitization, based on a sound and critical diagnosis, in most cases of asthma offers the patients a better future than other forms of treatment.

When, in 1941, the Allergy Clinic in Copenhagen was opened, the following three questions had to be taken into account:

1) How often is asthma an allergic disease?
2) How often will it be possible to demonstrate the etiological causes?
3) Will specific hyposensitization be effective?

The literature did not help us much. In the hands of reliable scientists the results of specific hyposensitization in asthma varied within very wide limits, improvement being stated in from 20 to 90 per cent.

Therefore, we set ourselves the task to apply such diagnostic procedures that a reliable allergy diagnosis was obtained, and to procure a material of patients which would clearly demonstrate the value of specific hyposensitization.

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Already in the twenties, the early Dutch allergy school (Storm van Leeuwen, Tissot van Patot, and Varekamp) advocated exogen allergens as the main cause of asthma, and on the basis of the anamnesis, cutaneous diagnostics, provocation tests, elimination procedures and several other

TABLE 1

Results of specific hyposensitization in 239 asthmatics, period of observation: 6—12 months (Bruun, 1945)

	Number of patients	%		Average duration of asthma
Without symptoms	50	20,9 %	= 88.2 %	7.0 years
Improved	161	67.3 %		9.1 years
Unchanged	27	11.2 %		11 6 years
Worse	1	0 5 %		
Total	239 patients			

examinations we arrived at the conviction that in most cases (probably all) asthma is an allergic condition, and that in most cases an adequate exogen allergen can be demonstrated as the etiological cause.

On purpose it was decided to treat all cases of asthma, whether complicated or not, in which an allergic condition was considered the basic factor, with specific hyposensitization, and to use this treatment as the [illegible] (period of observation: 6—12 months).

Secondly, the same patients and several additional cases (a total of 478) were reexamined after a period of observation of about three years, and some of the patients were treated with more than one series of injections. As might be expected, the good immediate results were not lasting, and after a lapse of three years the percentage of [illegible] dropped [illegible] specific [illegible] asthma-therapy, because in a control material Henriksen found a percentage of improvement of 52. It seemed, however, as if the results were improved if the patients were treated with repeated series of hyposensitization (Table 3), which may indicate that by a continous treatment over a period of several years the results might be improved.

Before this, however, the influence of the psychological factor in asthma-therapy had to be evaluated. To this purpose placebo examinations were carried out. For a period of 18 months house dust allergic asthmatics with odd case record numbers were treated with the specific

TABLE 2

Results of specific hyposensitization in 478 asthmatics, period of observation. 3 years (E. Henriksen, 1951)

	Number of patients	%	
Without symptoms	36	7.5 %	= 59.8 %
Almost without symptoms	38	7.9 %	
Improved	212	44.4 %	
Unchanged	108	22.6 %	
Worse	51	10.6 %	
Dead	33	6.9 %	
Total	478 patients		

TABLE 3

Results of specific hyposensitization in relation to the number of series of injections (E. Henriksen, 1951)

Number of series of injections	Number of patients improved	%
1	146	57.2 %
2	69	57.0 %
3	38	65.5 %
4	21	75.0 %
5 or more	12	75.0 %

extract, and house dust allergic asthmatics with even case record numbers were treated with placebo; from table 4 it becomes evident that specific treatment is superior to treatment with placebo. Erik Andersson, is his studies on the effect of cortisone and ACTH therapy in asthma, also made placebo experiments and arrived at the same figure: 4 out of 11 patients, i e. about one third, improved with placebo treatment.

These investigations demonstrate that when the patients are given the impression of being under adequate and proper treatment, one third

will state improvement, independent of what kind of treatment they have been submitted to. This must be borne in mind whenever a new form of therapy claims to give results in asthma.

In 28 patients we were able to carry out a kind of double control, as these 28 were first treated with placebo and then, after a suitable period of observation—with the specific allergen. From table 5 it appears that

TABLE 4

Control examinations of the specificity of specific hyposensitization (Bruun, 1949)

	Specific hyposensitization		Placebo treatment		Total
Without symptoms	13.6 %	78±4.3 %	3.7 %	34±5.3 %	
Improved	64.2 %		30.5 %		
Unchanged	18.9 %	22±4.3 %	54.9 %	66±5.3 %	
Worse	3.2 %		11.0 %		
Number of patients	95		89		184

TABLE 5

[illegible]

	Placebo treatment		Specific hyposensitization	
Without symptoms	0	21 %	2	75 %
Improved	6		19	
Unchanged	19	79 %	5	25 %
Worse	3		2	

that 22 out of 28 patients remained uninfluenced by placebo treatment, whereas in the same group of patients only 7 out of 28 did not improve after specific hyposensitization.

On the basis of Dr. Henriksen's observations that the results are improved by repeated series of injections, we started, in 1951, a continous form of specific hyposensitization, in the way that a continuation course of the strongest dose—generally 0,7 ml of a 1 : 100 dilution—is given once every second or every third week for three years. After

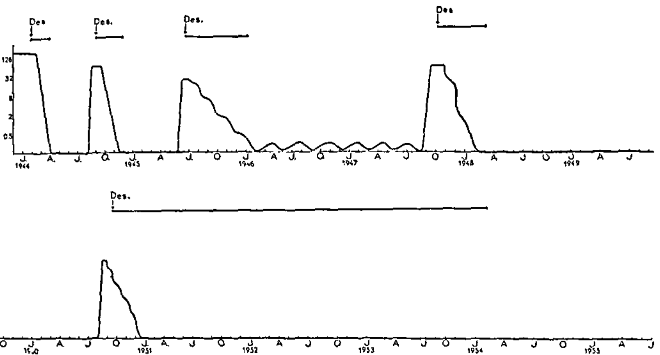
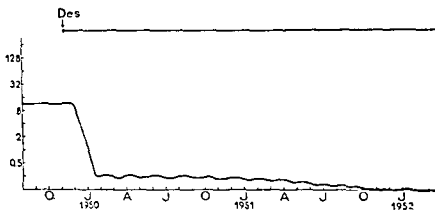


Fig 1

662/44 ♀*1890 Asthma since 1933: house dust allergy
Ordinate: average duration of asthma attacks (hours/month)
Des. = Specific hyposensitization
See page 29



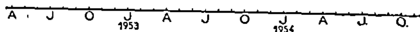
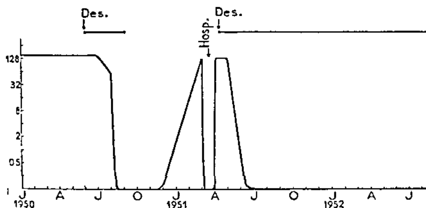


Fig 2

3248/49 ♂ *1911. Asthma since 1949· Allergy to feathers and house dust



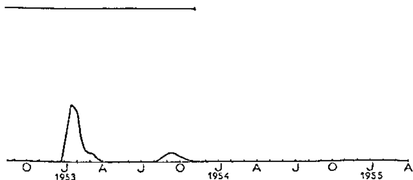
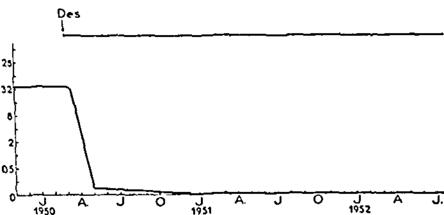


Fig 3

1798/50 ♀ *1913. Asthma since 1947. Allergy to house dust and feathers (and salicylates)



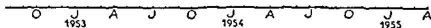


Fig 4

4022/49 ♂ *1920 Asthma since 1930. Allergy to feathers and house dust

Fig. 5

3260/45 ♂ *1925. Asthma since 1943· flour (baker)

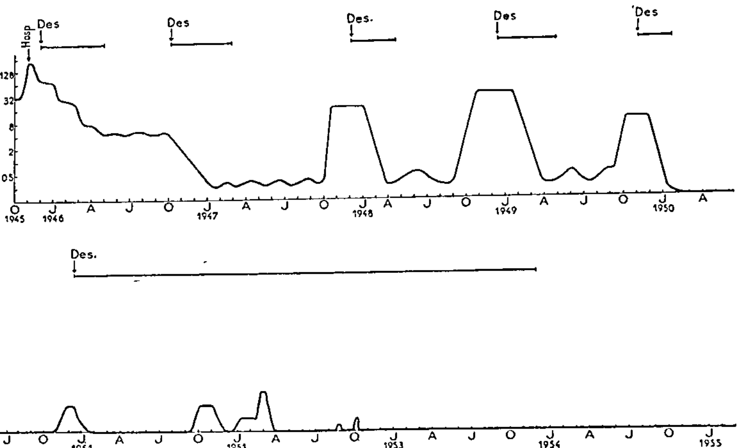
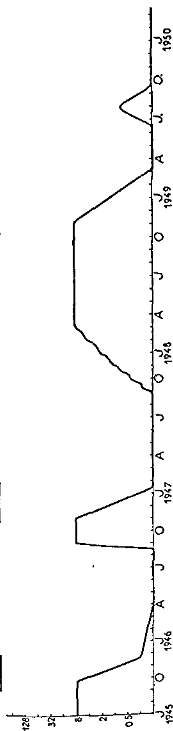


Fig 6

2269/45 ♂ *1907 Asthma since 1944: house dust allergy



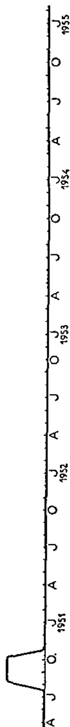
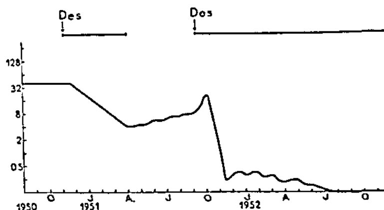


Fig 7

640/45 ♂ *1908 Asthma since 1924 house dust allergy



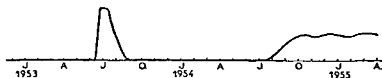
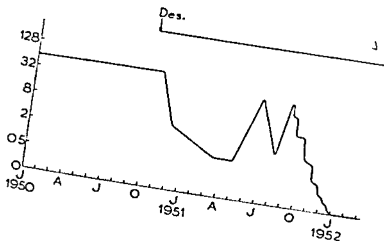


Fig 8

3852/50 ♀ *1883. Asthma since 1919· Allergy to house dust and feathers



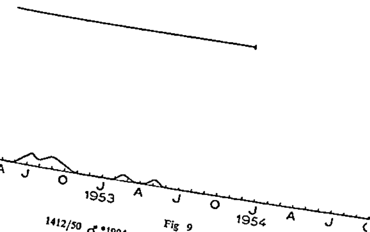


Fig 9

1412/50 ♂ *1904. Asthma since 1949 house dust allergy

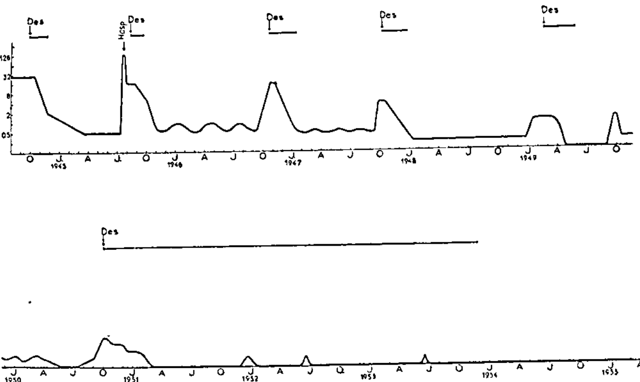


Fig 10

2572/44 ♂ *1901 Asthma since 1926: house dust allergy

three years' treatment the injections are discontinued, and the patients are kept under observation for a period of another three years. As mentioned above, this experiment was started in 1951 and, consequently, has not been finished yet, but on this occasion some preliminary results can be discussed. The definite evaluation must be postponed for another two years, or maybe even more. A total of about 5—600 patients are included in the experiment. To elucidate the asthmatic condition in each patient I have tried to make a graphic illustration, a diagram for each patient. In a co-ordinate system the average duration of asthma attacks per month forms the ordinate, and the time of observation constitutes the abscissus. When, for instance, a patient claims to have asthma for about one hour every night, the duration of his attacks is estimated at 30 hours per month. In another case the patient may state that he suffers from asthma constantly for 2—3 days, in connection with colds, and that he gets such colds every second month; in this case too, the monthly duration of asthma will be estimated at about 30 hours. From these examples it appears that the diagrams cannot give information about the type of asthma, but it can give you a rough idea of the effect of a long term treatment. On pages 19—28. such ten diagrams are reproduced. These ten have not been subject to any selection, they simply represent the ten first of the series. Better examples could be demonstrated, if they were picked out of the material, but it seems more suitable for the purpose to show you these cases that have not been selected.

From diagram 1 it will be seen that a patient with a severe bronchial asthma of a duration of 11 years can be regulated by specific hyposensitization. It will be seen too that the first attempts of hyposensitization (in February—April 1944, in September—December 1944, in June—December 1945, in August 1947—February 1948) resulted in relatively short periods of relief, but sooner or later she had relapses. [illegible]

treatment.

There is nor eason to go into details with the rest of the diagrams, as all necessary information can be obtained from the tables, but it must be mentioned that in one case, diagram 5, the therapeutical result was unsatisfactory. In this case the curve never reached the bottom-line, i.e. the patient never got free of symptoms. The patient is a baker with allergy to flour, and it seems reasonable to consider the daily exposure to the specific allergen to be too intense a factor to obtain a good result with hyposensitization.

As to the intradermal reactions it could be stated that after three

years of treatment they were definitely weaker than before treatment. On the other hand the vital capacity did not seem to be influenced by hyposensitization.

TABLE 6

Mortality rate in asthmatics, treated with specific hyposensitization, and in asthmatics otherwise treated

	Specific hyposensitization	Control material
Malmros & Rydberg, 1944	1 per cent	4 per cent
E. Henriksen, 1951	2.9 per cent	4 9 per cent

TABLE 7

Rate of invalid pension granted in specifically treated asthmatics and in asthmatics otherwise treated (E. Henriksen, 1951)

Specific hyposensitization	1.9 per cent
Control material	6.1 per cent

Besides the direct effect on the asthmatic conditions, some other factors must be dealt with, when you want to evaluate the benefits of specific hyposensitization. It is generally agreed that about 5 per cent. of asthmatic patients die from asthma. Of the many statistics, one of the latest will be quoted: McCracken, from Dr. Williams' Clinic at Cardiff, in a follow-up of 80 asthmatics over a period of 10—12 years, found 10 per cent died, 5 per cent from asthma. Already in 1944, Malmros & Rydberg, of Sweden, demonstrated a smaller mortality in specifically treated asthmatics than in controls. Henriksen made the same observation (table 6).

In addition, Henriksen found a remarkable difference in the number of asthmatics, who got an invalide pension, in the control group (6,1 per cent), and in the group of specifically treated patients (1,9 per cent), see table 7.

Finally, the value of the specific allergic diagnosis without other treatment besides that of elimination should not be overlooked, but is not within the scope of to-day's subject.

On the basis of these observations we feel it justified to recommend specific hyposensitization in asthma as a long term treatment. Whether three years of therapy is necessary, cannot be decided yet; probably a more individual treatment should be aimed at on the basis of the strength of the intradermal reactions. On the basis of our experience it seems reasonable to continue the hyposensitization until the cutaneous reactions become definitely weaker than before treatment. Although there are exceptions, the general rule is a correlation between good results and definitely weakened, intradermal reactions.

The effect of the specific therapy stands and falls with the right etiological diagnosis. It is not sufficient to demonstrate a positive cutaneous reaction; several other factors must be taken into account, when the allergic diagnosis is established.

Failures in specific hyposensitization are due to a wrong diagnosis —false reactions, unspecific reactions, etc.—or due to a neglect of a specific cause, which should be removed from the patient's environment.

At last it must be emphasized that specific treatment cannot cure the complications of asthma, neither bronchitis, emphysema, bronchiectasis, nor sinusitis. Too often the allergist is blamed because of poor results in conditions that have nothing to do with allergy. Therefore, we must try to get the patients to commence treatment as early as possible, before chronic complications have developed.

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FAILURE OF SPECIFIC DESENSITIZATION IN THE TREATMENT OF BRONCHIAL ASTHMA

by

P. J. VAN DER WERFF

The causal-aetiological treatment of bronchial asthma should be based on:

a) Systematic examinations, made to detect the determinants, which differ markedly in each individual case: allergic factors, endocrine disturbances, focal infections, etc.,

b) if possible, the elimination of these factors,

c) and as regards the allergic factors, especially air-borne allergens, hypo- or desensitization, (as avoidance of the inhalants is not always possible for practical and/or social reasons.

Valuable though it may be, this method does not always yield beneficial results [3, 12].

These failures are due to various causes:

1) *The incorrect selection of allergens*, owing to inaccurate or incomplete investigations and tests for air-borne substances and foods, which might be a possible cause of allergy in the patient concerned, will a priori result in the failure of specific desensitization.

As regards the house dust problem, it may be stated that preparation of an extract from dust obtained from the house of the patient, combined with examination of the dust samples for the presence of fungi, is essential in cases in which skin tests for allergy with standard house dust extracts are negative and the history of the patient suggests hypersensitiveness to dust. Utterly unexpected and unusual associations of fungi were observed in some exceptional cases (f.i.: Aleurisma Guilliermondi Grigoraki, Absidia ramosa (Lindt) Lendner, Botryosporium *longibrachiatum Oud., or: Thielariopsis paradoxa (de Seynes) v.* Hohn., Acrospeira levis Wiltsh.). We use the fine dust gathered from mantelpieces, furniture, etc., in preparing house dust extracts, rather than the coarse dust collected by the vacuumcleaner. Among other things, the latter often contains animal hairs and coarse particles of street refuse, substances apt to cause a marked non-specific secondary reaction, which may lead us into error in evaluating the results of skin tests for allergy, both those of the first skin test and those of the subsequent tests during desensitization.

The *chief factors*, which have to be especially taken into account in the Netherlands—if we wish to avoid omissions in examining patients

for allergens are: house dust; moulds; pollens; old kapok, bed-feathers, sea-weed, waste wool, oat-husks, dried ferns and Alp-grass for stuffing mattresses, pillows and upholstered furniture; mites; haystack and cornstack dust; animal dander; foods. We found no demonstrable allergy in about 6 per cent of the cases.

As regards occupations and trades, it may be stated in general that the most frequent and severe cases of asthma may be anticipated whereever vegetable or animal substances are used in industry and the microflora of spoilage fungi with fairly constant associations, specific of each of these substances, is present. [32]

2) *Incorrect indications* will inevitably result in disappointments. We shall briefly review some of the principal clinical pictures:

a) Detailed examination of the sputum and x-raying are essential in establishing a differential diagnosis in patients with asthma showing symptoms of bronchitis. [19]

Specific desensitization may be naturally be expected to be succesful in: *eosinophilic, non-bacterial bronchitis*, as it actually is a chronic asthma of allergic origin, marked by the production of a viscid, mucous, occasionally foamy sputum, which always contains a large number of eosinophils, whether or not accompanied by acute attacks of asthma.

Failures are bound to occur, when by an unsufficiently detailed examination specific fungus desensitization cure is administered *in cases of bronchial asthma, secondary to mycosis or thrush of the bronchi and lungs.* [22, 31] The internal source of allergens should be destroyed by medical or surgical treatment in these cases, irrespective of whether an active inflammation is involved or a silent growth of fungi has occurred in the respiratory tract.

There is a chance of failure when the wrong time has been chosen to start desensitization, viz. *in cases of chronic asthmatic condition with secondary infections by bacteria.* These cases usually show inflammations caused by Haemophilus influenzae, pneumococci, Staphylococcus aureus, Neisseriae or combinations of these bacteria. [25]

With a few exceptions, the asthma was either seen to remain unchanged or even to show frequent signs of aggravation in these patients, when antibiotics were administered *prior to* anti-allergic treatment. [20, 15]

The cause of this phenomenon continues to be obscure.

Specific desensitization has no effect on possible *bronchiectasis* associated with asthma, a frequent complication

b) Once a *substantial emphysema* has developed, possibly accompanied by cor pulmonale, desensitization will not result in its disappearance. This treatment will only be of use when the condition is associated with attacks of allergic asthma In our experience there is a considerable chance of general systemic reactions in these cases; we don't know why!

All this implies that complications should be prevented if possible by early anti-allergic treatment, preferably as early as the stage of vasomotor rhinitis, which so often precedes bronchial asthma.

3) *The incorrect use and/or too short a duration of specific desensitization* is conducive to failures.

The usual method, viz. the subcutaneous injection of increasing doses, whether or not under the protection of adrenaline, sympatol, antihistaminics, ACTH prolongatum and cortisone, may rapidly induce a state of hyposensitiveness in various cases of asthma with 'rush-desensitizing therapy'. [9] This treatment is especially useful in preventing relapses following the return of the patient to his home surroundings after hospitalization No satisfactory results will be obtained however, unless treatment with 2—3 weekly injections is continued for at least six months; another eighteen months, during which maintenance doses are given at increasingly long intervals, being required to obtain results positive both from the serological and clinical point of view.

This is especially true of patients allergic to seasonal moulds and individuals engaged in particular trades and occupations, such as farming, the baking trade, flour mills or the textile, wood and leather industries.

In our experience this only applies to air-borne allergens.

For we have never observed tangible results, obtained by subcutaneous injections against foods

Occasional treatment with skeptophylaxis or prolonged habituation or desensitizing by oral administration of gradually increasing doses [23, 27, 13] did indeed result in some improvement in scarcely 17 per cent of a group of 260 patients with characteristic food-allergy in our hospital On the other hand, psychogenic factors played such an important role in the not so many cases in which treatment was 'completely succesful' that even the results obtained in these subjects do not accurately reflect the true state of things. Therefore Willem Kremer, who devoted particular attention to the problems of food allergy for many years, believed these methods to be of little use in treatment.

Our own experience has not been sufficient to give an opinion regarding the value of spray inhalants [17] and oral methods in the treatment of inhalance-allergy [29, 2, 28] and Urbach's oral propeptane therapy, [30] the sublingual, [10] the intracutaneous [24] and the intramuscular methods of administration of allergenic extracts prepared from inhalants and foods.

Confining ourselves to desensitization against inhalants, the next cause of failure may be stated to consist in:

4) *errors of dosage*. Too small doses, may occur, as all liquid allergenic extracts decrease in allergenic potency, slowly in some cases, rapidly

in others; among other things, this depends upon the temperature at which the vaccine is stored and the type of fluid used in preparing extracts. Recently prepared liquid pollen and fungus allergenic extracts sometimes show a particularly rapid decrease even in the first days. *Clinically, this involves the danger that the first injections of such a* recently prepared vaccine might give rise to general systemic reactions. (When desensitization was administered in low dosage during a rather long period, this treatment sometimes has yielded excellent results).

Apart from the danger of systemic reactions, [5] in our experience a failure is most liable to occur when *too large doses* of the extracts prepared from pollens, moulds and yeasts are administered (cf. p. 40).

When patients are being tested or treated with drugs, regardless of the method of administration, danger is present. [7] Special mention should be made of this *drug allergy,* which sometimes, e.g. when using pulv. *rad. ipecac. and pulv. fol. digitalis, does, but frequently does not induce* a local wheal in skin tests for allergy. [11] Severe systemic reactions may occur unexpectedly in these cases, as we saw in skin tests with aspirin and diphantoin, and also observed in the case of a worker employed at a pharmaceutical factory, who was hypersensitive to neo-arsphenamine.

5) Likewise *an incorrect evaluation of the results of skin tests for allergy during desensitization* may provide unpleasant surprises. One should be careful in evaluating the reliability of local wheals as a sole test of the stage of hyposensitiveness or desensitization respectivily. Like others, [6b] *we frequently observed, that an initial increase of the local* reaction in the early stage of treatment was followed by a decrease, accompanied by a progressive improvement of the clinical symptoms of allergy. Undoubtedly this was not true in all cases In that event the skin reactions continued unchanged or disappeared entirely, regardless of the result of treatment. [16, 4, 18, 1]

Thus some cases showed an improvement without skin tests differing significantly from the initial reactions, whereas the positive skin reactions even decreased or disappeared in others, which had to be defined as failures from the clinical point of view. The statement that one should be careful in increasing the dosage in the case of a markedly strong skin-reaction continues to apply in clinical cases. One should be double careful in the event of none, only a slight or a delayed reaction.

It is virtually impossible in practice to determine the quantity of circulating serum reagins and possibly that of blocking antibodies at regular intervals. In addition the latter are not always produced, not even when large doses can be tolerated. This is true e g. in the case of house dust and in that of the lignase- and cytase-producing fungus Trichoderma viride Pers. ex Fr., as I was able to observe personally.

When the variations in the results of the skin tests for allergy made to verify the effect of treatment during desensitization are studied in the light of current serological knowledge, they will after all be understandable to a considerable extent.

Without wishing to minimize the work of other investigators in this field, attention may be drawn to certain milestones: the introduction of specific desensitization in human medicine (Freeman, Noon, 1911); the demonstration for the first time of inhibitors in the blood of asthmatic patients with fungus, feather and cat's hair allergy (Storm van Leeuwen and Kremer, 1927, Kremer, 1932); the rediscovery of these inhibitors in the blood of patients with hay fever (Cooke c.s., 1935); the determination of the nature and point of action of antibodies inhibiting the reaction (Van Dishoeck c.s, 1942).

In the opinion of Van Dishoeck,—and we are in complete agreement with this view—, the decrease of the sessile tissue reagins and an increase of circulating reagins (state of hyposensitiveness) is followed by the actual desensitization caused by the blocking antibodies, which as he showed, act upon the reagins and which he therefore called '*antireagins*'.
6a 6b

It is conceivable, that in some cases of failure there may be a likelihood of a compensation situation occurring in an occasionally permanent intermediate stage between the increase in reagins and the production of antireagins, including the possibility of other, so far unidentified, factors.

6) Accordingly, excluding other causal determinants, there are a number of *patients, who are unable to acquire a state of hyposensitiveness or desensitization* In these cases there was a certain tolerance to the allergens. This was shown even by adequate large dosage of allergens, subcutaneously administered, although the air-borne allergens were not tolerated in the exposure and inhalation-provocative tests and likewise no definite improvement subjectivally and clinically resulted.

7) Moreover, there are patients, who, by causes hitherto unknown, have *an intolerance to the allergens involved*, even when treated with extremely small doses and with protective drugs

Despite all our precautions taken in asthmatic patients with inhalance allergy, symptoms persist in at least one-third of the total number of [illegible]

an [illegible]

Failures hardly ever occur in animal experiments, although individual and generic quantitative variations may be observed.

There are much more doubtful factors in men, however, so that the risk of a large number of failures must be taken into account.

The realization and study of these failures are of particular importance, as they may possibly put us on the track of the other causal factors which in addition to sensitization play a rôle in bronchial asthma.

SUMMARY

The causes of failure in treatment of bronchial asthma by specific desensitization are reviewed.

Failures may be due to:

the incorrect choice of allergens,
incorrect indications,
use of an incorrect method of specific desensitization,
incorrect evaluation of the results of skin tests for allergy,
inability of the patient to acquire a state of hyposensitiveness or desensitization,
intolerance to the allergens involved.

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DISCUSSION

SOME PROBLEMS CONCERNING THE RESULTS OF TREATMENT WITH SPECIFIC HYPOSENSITIZATION

by

HELGE COLLDAHL

Three factors are of special importance in the treatment of asthma apart from the attacks They are specific hypersensitivity, bronchial infection and focal infectious processes

It is very important to stress, when judging the result of asthmatic treatment, that the asthmatic troubles in a special case are often caused by multiple factors and that the result of the treatment depends upon how important factors could be more or less eliminated by the treatment.

The effect of specific hyposensitization must therefore be dependent upon the

therefore think it is of extreme value to investigate by the help of provocation tests and so on as to how important the specific cause is in a special case.

In a series of 387 asthmatic patients investigated 1950–1953 at the allergy laboratory of the medical clinic of the University of Lund, Sweden, there was indication for specific hyposensitization in about 25 per cent. (Lund is a small town, most of the patients come from the country around.)

Of the 387 patients 229 (59 per cent) showed a positive skin test while 158 (41 per cent) showed a negative. 43 per cent of the patients with positive skin test gave a positive provocation test The best indication for giving specific hyposensitization in our opinion is a positive provocation test

The patients to whom specific treatment was given have also received other forms of therapy. Of these patients I have had the possibility to follow 53 for 1—3 years. The specific treatment was continued during a long time, 2—3 years 47 per cent had no troubles or were very much improved, 19 per cent much improved, 19 per cent improved. In 4 per cent no improvement occurred. In 5.5 per cent it was impossible to carry out the treatment and in 5 5 per cent the patients declined to complete the treatment.

Thus a result of the combined therapy was obtained in 85 per cent.

I think nobody can deny the effect of specific hyposensitization in a case where

result

ted as

have

been completely eliminated, but the importance of the specific factor was only

slight and other factors were of much greater importance. Combined treatment is often necessary. For the successful treatment of asthma it is important that as many different etiologic factors as possible are detected and eliminated or treated. Of special importance it must be to treat or eliminate the most significant causes.

Many authors have considered it important to have a control material when judging the results in cases where specific treatment had been given. Some of these authors have as control material used cases, where a specific sensitivity had not been detected Under such circumstances the control material, according to my opinion, cannot easily be compared with the group where specific factors are of importance. The groups are unlike If one wishes to have a control material it is necessary for such an investigation to choose cases as similar as possible in all respects and to treat only every second with specific treatment. This was done by Bruun 1949. I think that a large investigation in that way would be of great importance.

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SPECIFIC DESENSIBILIZATION

by

A. W. FRANKLAND

There are very many reasons why when desensitization has been decided upon the results are not as good as might be expected I should like to mention one aspect only and this is concerned with the dosage. Quite often and possibly because of the fear of general reactions, but also because of the large number of injections required, a sufficiently high dose is not reached in the course of desensitization This was well shown in a recent controlled trial carried out in patients with seasonal hay fever (Frankland, *Acta Allerg* 1956 in the press.)

REPLY TO DR FRANKLAND

by

P J. VAN DER WERFF

I wish to thank Dr. Frankland for his supplementary comments. Our experience has indeed also shown that administration of *too small doses* may ultimately result in hyposensitiveness In using this method, however, too much valuable time is wasted unnecessarily and practice has shown that in this event the patient (or the physician) sometimes becomes discouraged without need and too soon.

When the *dosage is too large*, the case is quite different:

1) this involves the risk of a more or less severe general systemic reaction and

ness.

It may possibly be worth mentioning that in the past years I treated three patients who had a shock due to administration of too large doses; this immediately resulted in a state of hyposensitiveness in two of these patients; the third had become intolerant, however, as was shown by administration of the weakest dilutions.

Case 1. Miss C F., aged 22, a seamstress, hardly able to work as a result of severe

nor inhalation tests with standard house dust or other fungi had been positive) The responses in the positive skin tests were markedly strong; the 4th injection given in the course of desensitization was seen to result in a local reaction measuring 2 by 3 cm. and mild symptoms of vasomotor rhinitis. The fifth injection resulted in a severe dyspnoea, appearing within a few minutes, and a state of shock, which persisted for 3 hours Subsequent skin tests and inhalation tests were negative, even when increasing doses were administered. Since that time she has had no further attacks of asthma. Follow-up 5 years.

Case 2 Mr W. den H., aged 41, an electrician, affected with very severe asthma, which had rendered him unfit for work for 6 months past. The patient showed a

mucosa, the sixth injection, however, gave rise to a very severe shock. The patient subsequently continued entirely free of symptoms for well over one year and six months The symptoms then gradually increased again, an improvement being obtained by a prolonged course of desensitization in low dosage.

Case 3. J. H., aged 17, employed at an old metal, rag and waste-paper store, affected with severe progressive asthma and vasomotor rhinitis Markedly allergic (both serologically and clinically) to industrial dusts and fungi The first two injections gave only one + local wheal; the third injection of the 1 per cent vaccine, administered in increasing doses, immediately resulted in vasomotor rhinitis,

vaccine resulted in continued attacks of severe dyspnoea, persisting for 2 days Three injections of a placebo failed to elicit any response, but administration of a 1 : 100 dilution was followed by shock, marked by general distress, severe

dyspnoea and a brief collapse. A placebo was given for a few weeks, followed by administration of a 1 : 100,000 dilution, resulting in a marked local reaction, mild dyspnoea in the evening and a mild degree of vasomotor rhinitis appearing the next day

I previously reported the case of a patient with hay fever, who initially showed marked local reactions, in view of which fact great caution was used in desensitization. In the third year the local reactions had diminished and the doses were increased somewhat more rapidly, which unexpectedly resulted in a very severe state of shock. The first subsequent injections gave rise to local reactions, which were as marked as they had been at the beginning of desensitization cure.

SPECIFIC TREATMENT OF ASTHMA

by

R. ALEMANY-VALL

The treatment by pollen is quite efficient at the first stages of the pathologic condition, these stages are counted by seasonal years when only conjunctivitis [illegible]
evident rhinitis may remain present, in spite of specific treatment.

[illegible]
has been followed.

Patients sensitive to Platanes (Plutanus orientalis) suffer from rhinitis and asthma, improved by the treatment, although, generally, not quite so much, as is the case with those sensitive to gramineous plants; this occurs also in those sensitive to 'Parietaria officinalis', of which many cases may be seen on the Mediterranean Coast; this depends on the larger diffusion of pollen in the local ambient air of the patient, in proportion to neighbouring plants When there is a large quantity of pollen present, the treatment may even give opposite effects.

We administer injections on alternate days, or one every week or two weeks per tenth parts of 100 – 10,000 units, this specificity is the clearest and most evident of all allergic affections. Cutaneous reactions remain positive even out of season — these reactions, to certain pollens, will recur even years afterward in patients without any crisis or very slightly affected (Parietaria).

Those sensitive to Chenopodium Album respond very well to the treatment. We found this pollen not only at the beginning of autumn, but also in summer, spring and even in winter.

We have not seen pollinic crises only appearing during the night; we have seen, however, night-crises in patients suffering from daily crises; we have seen hardly any pollen in the house of the patients, and found little at night on the slides.

We saw cases sensitive to the pollens of Cosmos, Aster, Gladiolas, Daisies, etc. in florists, showing large cutaneous reactions and even focal reactions by simple scarification, with pollen above them We do not advise a desensitizing treatment for these patients living in contact with these plants and whose crises begin already in June.

Those sensitive to both pollen and dust when the latter is widespread in the ambient air of the patient, but only in months of intensive pollen-formation, specially in Parietaria (April – May or May – June) must be treated only with pollen, not with dust; when these two months have passed, the dust does not act any more, although pollinic crises may occur, less intensively, on account of there being less pollen.

We have not often seen patients sensitive to hairs; these always improve under treatment, provided that the ambient air is not too full of hairs. In our service of Allergy in the Medical School, the separation of various flour-protein was obtained (proteose, globuline, gliadine and wheat glutenine; also albumin and rye-globuline) which have been administered as diagnostic and therapeutic means, for asthmatic bakers; we have even obtained pseudopodic reactions in them; in general, proteose and globuline were those substances which reacted most but the therapeutic results were relatively poor.

ASTHMA AND RHINITIS CAUSED BY FUNGI

by

R ALEMANY-VALL

The sensitivity may be limited exclusively to fungi, or be a concomitant of other forms of sensitivity.

extracts of the fungi which had reacted on the skin, and these injections give good results. The cures must be repeated sufficiently. The case of the patient is clear: nasal reactions may be stimulated by contact with the respective fungus; there always are nasal eosinophiles.

2) *Sensitivity to both fungi and dust:* in persons living in buildings, housing cereals, stores; etc. The desensitization with fungi and, at times, with dust is good; the treatment must be frequently repeated.

3) *Sensitivity to fungi and flour in bakers:* The treatment is bad and may even produce opposite effects; it is necesary that the patient should be removed because some of them cannot remain even a few hours in these surroundings; we have always found there Mucor, Penicillius, etc. If penicillin is administered by injection, intensive asthmatic crisis may occur — although not necessarily, nor always — and we have seen one with a subcutaneous emphysema.

4) *Sensitivity to fungi in patients with bronchitis infections and asthma·* These conditions do not respond to treatments with fungus-extracts, but yield to bacterial vaccines; upon the administration of penicillin extemporaneous asthmatic

reactions may still occur, but they will fast disappear. Skin reactions to fungi and bacteria may disappear in climates of high altitude and reappear or even develop into asthmatic crises, when the patients go to lower places with a more damp climate than they were accustomed to.

5) *Sensitivity to fungi in patients who exhibit small fibrous-pulmonary lesions* with normal blood sedimentation and general well-being; an intensive and repeated asthma, even without initial rhinitis. The condition is improved by the administration of fungus-extracts, tuberculin and similar products. When the patient leaves the damp climate, his asthma quickly disappears.

6) *Sensitivity to fungi and dust in patients, with small and reduced fibrous lesions:* a clear case of rhinitis and asthma in damp houses with visible moisture on the paper of the walls, although we did not always find fungi on these walls. It will be necessary for the patient to change his living quarters, because, if not, unpleasant — and even fatal — consequences may follow. If the patient goes to live in well-aired, sunny houses with communication with free air, the asthma will quickly disappear.

Para-allergic reactions will often occur.

[illegible]

patients cannot live in certain climates considered damp, although sometimes there are no skin-reactions to fungi. These patients will improve, when they live in temperate semi-altitudinal climates in dry places, protected from winds. Treatment with fungi will give no results.

In damp climates where humidity collects on account of local geographic conditions there will always be a higher percentage of asthmatic patients whose condition is due to fungi, than in those in which there are open spaces and frequent winds.

In country houses, sufficiently far from stores of grain, etc. even if Mucor, Penicillium, Alternaria, etc. may be found, their proportion will by far not be the same, as those of rooms in city dwellings. Fungi are abundant in granaries and stores, etc. We have even found them in operating rooms of modern hospitals.

H. J. TEN CATE

Specific hyposensitization is a prolonged and expensive treatment. It seems only justified to inhalant allergens which cannot sufficiently be eliminated like pollens, mould spores, house dust antigen and sometimes occupational allergens, like cow hair and hay dust with farmers. The results are often excellent, especially with pollens and mould spores but some patients experience only partial or no benefit at all. Before undertaking this treatment one should be quite sure of the existence of bronchial sensitization to the allergens chosen for desensitization.

If the history corroborates the positive skin test, evidence of bronchial sensitization exists.

A positive skin reaction not confirmed by the history needs further investigation before starting hyposensitization treatment.

A simple method to demonstrate bronchial sensitivity to inhaled allergens consists of inhalation of aerosolized allergenic extracts The effect can be demonstrated by recording the vital capacity before the procedure and several times afterwards at 4 minutes intervals

We obtained the following results on asthmatics when the history was not considered:

Number of pat	Skin test	Inhalation results		Percentage	
		Positive	Negative	Positive	Negative
249	Strongly pos	147	102	59	41
183	Mildly pos.	65	118	35,5	64,5
88	Negative	0	88	0	100

When the history regarding specific sensitizations was considered on patients with positive skin tests the following results were obtained:

Number of pat. with pos skin tests	Results of history	Inhalation results		Percentage	
		Positive	Negative	Positive	Negative
143	Positive	107	36	75	25
83	Doubtful	38	45	46	54
177	Negative	39	138	22	78

HOUSE DUST ALLERGEN(S) AND HYPOSENSITIZATION

by

KATE MAUNSELL

I. HOUSE DUST ALLERGEN(S)

The pattern of bronchial asthma is constantly changing, owing to phases in the degree of sensitivity of the individual and to environmental changes due to season and region or such irregular events as floods, bombings and upheavals in daily life. The composition of house dust reflects these environmental changes and is therefore, in part, responsible for the changing pattern of asthma.

The material from which house dust is derived may be of intramural or extramural origin, but house dust is not more dirt, a dead mass of inert material. It swarms with living organisms, from 10,000 to several millions spores of fungi can be found in one gramme of dust, the number of bacteria is equally large and mites, too, may live in house dust. All these micro-organisms either act as specific allergens themselves or, by virtue of their enzymes, break down complex organic matter into simpler compounds, thus making or modifying house dust allergens.

The materials which are broken down derive from building and furnishing materials of animal and plant origin, such as horse hair (used not only for upholstery, but also for ceilings in old houses), glue (the main component of sizes), feathers, cotton, wood and so on. House dust further contains scales from man, animals and insects, and particles blown indoors or carried in on shoes or garments, such as plant debris, pollen and plant debris, pollen and soil, and also particles of ash, carbon and tarry matter, due to atmospheric pollution by fires. Such is the conglomerate of house dust and several hypothesis are possible as to the origin of the house dust allergen(s).

1) House dust allergen(s) may be regarded as mixtures of specific allergen(s) deriving from these materials, either in their natural state or after being processed by industry.

2) In addition to this mixture there may be also one common substance which occurs during the phase of the breaking down of organic materials from different sources

Standardization

The lack of a good method of standardization is the major difficulty both in comparing samples of house dust and in estimating fractions

from any one single sample Rockwell et al (1947) found no correlation between the skin-reacting substances and total nitrogen or phosphotungstic-acid precipitating nitrogen. Other authors have confirmed this. Woodhouse (1954) recommended the Gel-diffusion technique. However, the method of skin-testing is still used in analyzing the potency of house dust, although it lacks the precision essential in research. The maximum of accuracy possible is obtained by intradermal skin-titrations and determination of a 'threshold-titre'. This is the reciprocal of the lowest dilution of any one extract to give a positive reaction. Every fraction is tested against a standard fraction and a ratio established between the two. The ratio of both threshold-titres is referred to as test-index. It varies in different individuals to some extent. Each sample was therefore tested on at least four dust-sensitive individuals and the mean of the 4 test-index figures obtained.

House dust from different houses

It may be that the potency of house dust is influenced by the degree of humidity of the houses concerned, and this again may depend on the soil on which the houses stand. Such a possibility was suggested by Vallery-Radot (1949) who observed the frequency of housedust allergy in persons living in houses built along the banks of the Seine. Harsh (1952) noted that in the damp coastal areas of San Diego, California, with a relative humidity averaging 75 per cent, the number of patients suffering from respiratory allergy to house dust was high. In contradistinction, in an extremely dry inland area, below sea level, with an abundant crop of pollen, the main allergy was represented by pollen sensitivity. He believed that humidity rendered house dust and possibly other inhalant allergens more allergenic. In London, which is built mainly on clay soil, the onset of house dust allergy occurred more frequently in persons living in houses built on a relatively low level near waterways (Maunsell, 1952)[1]. Ordman, (1952, 1955) drew attention to the fact that in South Africa, in respiratory allergy of the perennial type (which included house dust allergy but excluded pollen allergy) a combination of high atmospheric temperature and high relative humidity in constantly narrow range seemed to be the significant climate factor. Further pursuing this question I obtained house-dust from different parts of England, all collected in September 1954. A wide variation in potency was shown, confirming the results of Rockwell et al. (1947) The strongest sample, No. 39, of the present series came from an extremely damp London house, with cracked walls, and damaged dampcourse, built on a sloping clay soil. The average test-index of the crude dust antigen

[1] Confirmation of this observation came from Milan (Fior and Teseo, 1955).

No. 39 was 250, whereas the test-index of dust from well preserved houses in different parts of England ranged only from 2—30.

Sample 39 and 8 other samples have been examined for their mould content by Mr. R. R. Davies, and preliminary results showed that the total colonies of moulds grown per gramme of house dust on malt agar varied widely. Sample 39 yielded 23,200,000 colonies of Penicillium, whereas the 8 samples from drier houses in various parts of England yielded only from 60,000 to 1,100,000 colonies of Penicillium (R. R. Davies, 1955). This result indicated that conditions favouring the growth of Penicillium favoured also the development of the dust allergens. No evidence, however, has been obtained for regarding the Penicillium allergen as identical with the house dust allergen.

Fractionation

In order to learn more about the active particles of housedust fractionation of single samples is essential.

Mechanical fractionation separates the finer from the coarser particles of house dust. As a result of gravity the smaller, light particles float in the air a considerable time before reaching the ground. According

TABLE I

Rate of fall of spherical particles of unit density in air at 20 degrees C. and one atmosphere pressure

Reactivity	Diameter microns	Terminal velocity cm /sec.
	0.2	0.000225
	0.3	0.0042
	0.5	0.0010
	1	0.0035
	2	0.0128
Strong	3	0.0275
	5	0.078
	10	0.30
	20	1.2
	30	2.7
	50	7.2
	100	25
	200	70
Weak....... ..	300	115
	500	200
	1000	385

from C N Davies (1954)

to Stokes' law particles of one micron diameter fall at the rate of only 0.0035 cm. per second, whereas particles of about fifty microns diameter fall at the rate of 7.2 cm per second. Unfortunately, the smaller particles which float longer in the air and are therefore inhaled for a longer period are far more active than the larger ones. This was shown by passing house dust through a sieve with a mesh of 76 microns diameter Extracts from the fraction passing the sieve produced much stronger skin-reactions than fractions from the extracts retained by the sieve. The particulate matter can also be graded into sizes by allowing the particles to settle in chloroform or benzene, the heavier particles settling more quickly. Again it was found that the lighter particles gave the stronger reactions. (Table I).

Biochemical fractionation of house dust antigen is based first on the adsorption of the allergen of house dust by suitable adsorbents, secondly on the retention of the active molecules by dialysing membranes and thirdly on their precipitation by acetone. These properties have been made use of in the various methods of fractionation. The method described by Rimington et al. (1947, 1952) followed the process outlined by Sutherland (1942) and carried it some stages further. House dust was soaked with dilute ammonia and the extracts treated with sodium benzoate (20 grammes to 1 litre). The addition of hydrochloric acid (one part concentrated acid to five parts of water) produced a precipitate of benzoic acid which adsorbed the active material. This was filtered of and the benzoic acid was dissolved by the action of acetone. The dark material which was left as a precipitate could be dissolved in water and precipitated with aqueous acetone (25 to 80 per cent). The precipitate obtained at this stage was termed 'standard crude antigen'.

Further purification was obtained by dialysis against citric acid, and the ash-free material was again precipitated by acetone. This purified material was highly active, but protein tests were negative It contained 6 per cent nitrogen. When this compound was hydrolysed with weak acid, the carbohydrates were rapidly broken down and amino-acids liberated. Only when substantial liberation of amino-acids occurred was the biological activity destroyed. It was concluded that the polypeptide moiety was the essential part of the structure of the allergen.

The same type of molecule (polysaccharides linked with polypeptides) has been found in the active fractions of fungal cultures, as for example Penicillium (Stillwell et al., 1947) and cotton (Cayton et al., 1952).

Samples of house dust obtained from a firm of cleaners have been subjected to chromatography (Rimington et al, 1947). Galactose was the only sugar composing the polysaccharide portion. Partition chromatography to identify the amino-acids appearing on hydrolysis revealed the simple monoamino-acids with the exception of histidine and

lysine. The aromatic amino-acids, such as tyrosine and phenylalanine, were mostly absent.

Chromatography has now been carried out also on house dust obtained from single houses. The results have confirmed in the main the previous findings. In some samples, however, other sugars—glucose and mannose—appeared, apart from galactose

Partition chromatography using, however, butanol-acetic acid water instead of collidine as the second solvent, showed again that glutamic and astartic acids were present in all samples, and that the aromatic amino-acids such as phenylalanine and tyrosine were only found in a few samples.

Considering the likelihood of wool and hair fibres being present in the original dust, it is remarkable that arginine and cystine were found in traces only (Rimington) or else were absent (present series).

Inhibition test

The type of molecule described here resembles the blood group specific substances (Morgan and King, 1943) which are in the tissues and secretions, such as saliva, of many animals and of human beings of group A and B Group specific factors inhibit the agglutination of red cells by the corresponding sera. It seemed of interest to see whether the dust allergens would behave serologically in a way similar to the group specific factors.

> Serial dilutions of one unit of serum in normal saline were mixed with one unit of standard crude antigen (10 mgm in 1 ml of normal saline). Control serial dilutions of one unit of serum in normal saline were mixed with one unit of the appropriate red cells in a citrate suspension, and kept at 37 degrees centigrade for 30 minutes. The titre was expressed as the reciprocal of the greatest dilution of the sera causing agglutination.

Inhibition of the ABO agglutination by the dust allergen was shown, although the inhibitory activity was of a lower order than that shown by the blood group specific factors (Rimington, Stillwell, Maunsell, 1947). Binaghi (1950) confirmed this inhibition of red cell agglutination by house dust allergen(s) and reported this finding also in the case of related inhalants, as e.g. cotton and feathers. He believed that there was a close relationship between the strength of the inhibiting and the skin-reacting properties of the allergenic solutions.

The consequence of a hypothesis that house dust allergen is related to blood substances would be hyposensitization of dust allergic patients with human serum or horse serum. Such hyposensitization with human

serum was started but was given up on account of the danger of homologous serum jaundice (Maunsell 1944). Horse serum injections appeared too dangerous. Therefore the less harmful house dust is still chosen for hyposensitisation.

II. HYPOSENSITIZATION

In hyposensitization either extracts of house dust (Bencard) or crude dust antigen (Domogen, Duncan) was given. In the case of Domogen heat sterilisation was carried out as it had been shown that heating up to 100 degrees C. on three successive days did not destroy the skin-reacting properties There are certain advantages in the choice of house dust for immunization. Even if the hypothesis of a common dust antigen is not accepted, there is good reason to expect that such an extract will desensitise against feathers, horse-hair, moulds and so on. The risks so often evident in pollen immunization are practically non-existent in dust immunization. Local reactions occur and may be painful, but usually the infiltration dies down after one or two days. Attacks of bronchial asthma are rare, much rarer than after injections of bacterial vaccines

[illegible] e lines generally accepted [illegible] over a period of 2 years. [illegible] 0.1 ml (dilution: 1gm in 1000 ml), injections being increased by 0.1 ml up to 1 ml, followed by 1 ml as maintenance doses at longer intervals up to 1—2 years.

In cases treated, the skin reactions decreased and often became negative. Not always, however, did a negative skin reaction mean freedom from attacks.

A blocking antibody developed during treatment. It was, however, much weaker than the blocking pollen antibody occurring during hyposensitization. The mechanisms of the two immunizations seem to differ. It may be that the main effect of dust hyposensitization is adsorption of the comparitively small molecule of the dust antigen to the larger molecule of the globulin antibody After some time the allergen may be freed again. This would explain the short duration of the protection.

70 per cent of cases treated enjoyed marked improvement during their treatment, and half of them for many years later. The others relapsed when treatment had subsided. In evaluating results it should be borne in mind that the dust-sensitive patient with asthma is also prone to infections and their adverse effects on the asthmatic subject, and to emotional stimuli. Hyposensitization with dust, if successful, controls only one side of the whole syndrome.

In some cases it is possible to obtain better results from mixtures of

dusts with moulds or with weak bacterial vaccines, and such combinations must be decided in connection with the patient's history. In other cases it may be better to use a special source of dust, again depending on the history. In all cases, however, treatment should be combined with precautions and patients should realize the risk of inhaling air strongly polluted by house dust.

SUMMARY

The potency of house dust varies in different houses. The strongest sample came from an exceedingly damp house, and had an excessively high content of Penicillium spores.

Mechanical fractionation of house dust showed that the finer particles, which float longer in the air, were more active than the coarser.

Biochemical fractionation demonstrated that the active molecule consisted of a linkage of polypeptides with polysaccharides and that the activity resided in the polypeptide moiety.

Chromatography showed that the polypeptides consisted mainly of the simpler monoamino-acids and the carbohydrates mainly of galactose.

The type of molecule resembled the blood group specific substances.

The skin-reacting properties of the crude dust antigen(s) were not decreased by heating to 100 degrees C for thirty minutes.

70 per cent of cases found relief by hyposensitization with house dust extracts.

Hyposensitization should be carried out over a period of several years, and the best results may be obtained with house dust from a highly active source.

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DISCUSSION

DESENSITIZING TREATMENT WITH DUST

by

R. ALEMANY-VALL

We used, for purpose of the treatment, ordinary commercial dust and that obtained from cleaning doormats on industrial premises; we used, however, preferently the dust collected in the house of the patient himself, especially in his bedroom. We gave to the patient one or two injections per week, we never left him for 12 days without an injection The injections were diluted at the beginning, and more concentrated afterward. If the treatment is interrupted round the beginning, the trouble will recur, it does not happen, however, after five or six months. The doses must be progressive and injected in different places; the same dosis, repeated, cannot produce a cutaneous reaction, but exercise a good influence. The reactions usually diminish

Rhinorrhea is usually the first to diminish and disappear; sneezing will last a little longer and will not come in fits, but isolated and divided during the day; the most permanent condition will be nasal obstruction.

Skin reactions of inflammatory type, appearing belatedly, will give trouble to the patient, but may improve very transitorily As results of the dust-injections, intercutaneous nodes may rarely sometimes appear; they will have a clearly defined tendency to suppuration without fever or malaise; on the contrary, they exercise a beneficial influence on the illness, because the rhinorrhea and asthma disappear in a few weeks We have seen the inflammatory nodes in ordinary asthmatic patients after intradermic injections of microbial vaccines, with a good ulterior effect on the illness. Their biopsy and microscopic examination (Dr. Albantara) permitted us to see dispersed eosinophile cells together with neutrophile leucocytes having a tendency to suppuration.

We have scattered the dust of these bedrooms in media for fungi both in general and banal, and they did not produce any reaction on the patient's skin. We used aqueous extracts or these extracts already concentrated in vacuum or those resulting from the evaporation by electric fan in colodion thimbles; they were dialyzed with cellophane paper. The portion called 'proteinic' was separated from the hydrocarbonated, exposing the watery extract to the action of a hydrochoric solution in boiling for 3 hours, on different days.

Other extracts had been exposed to a temperature of 55°—60° C during one hour, and others even to 95° C for several hours, the extract has kept, in both cases, its reactionary activity on the skin. We have sometimes obtained a positive skin reaction both with the liquid which went through the cellophane and the one that did not. We finally used, for the extracts, Seitz's filter, with good skin reaction on the patient. We proceeded with a pH of 7,5—8.

Although the nitrogen value (index) does not show with absolute certainty the value of the extract, our chemist from the Medical School had determined

the total nitrogen and proteic nitrogen by means of phosphotungstic acid; there was, as an average, 1.241 mgm. total nitrogen and 0.0560 mgm. proteic nitrogen per c.c. in the dust found in the rooms of the patient.

The standard dust of an industry working for the cleaning of rugs and mats in Barcelona contained 0.2800 mgm. total nitrogen and 0.0420 mgm. proteic nitrogen per c.c.

H. J. TEN CATE

Allergy to the house dust antigen is one of the main causes of asthmatic and rhinitis attacks in the Netherlands. 112 out of 152 asthmatics examined at the Groningen University Clinic for Internal Medecine (Chest department) demonstrated positive skin reactions to allergens, 100 out of them to house dust extract.

35 normal persons out of 106 normal controls demonstrated positive skin tests, 24 to house dust extract.

91 asthmatics out of 169 asthmatic patients with a strongly positive skin test to house dust extract demonstrated a positive inhalation reaction to an aerosol of house dust extract, which was inhaled, (54 per cent).

25 patients out of 70 patients with mildly positive skin tests to house dust extract reacted positively after inhalation of the house dust extract, (36 per cent).

In order to demonstrate the increasing bronchial tolerance during subcutaneous hyposensitization to house dust two hospitalized asthmatic patients were frequently exposed to house dust aerosol. They received daily house dust extract injections in increasing amounts. Blocking antibodies according to the technic of Kate Maunsell could be demonstrated.

Pat Date	House dust extract in mgm subcutaneous	Vit cap	House dust extract in mgm aerosolized	Decrease Vit cap %	Blocking Antib
V-R 8/8/1952	0	2150	30	30	Blocking index 0
19/8	15	2500	36	9	
29/8	42,5	2250	45	38	
10/9	1087,5	2525	75	50	Blocking index 2
V-V. 6/8/52	0	2600	18	81	Blocking index 0
16/8	1,65	3350	9	0	
19/8	8,4	3300	30	15	
22/8	25	3300	30	9	
30/8	91	3450	60	50	Blocking index 2—4
5/9	466	3450	60	0	
6/9	Discharged from hospital				
14/10	1006	3500	30	12	
25/11	1606	3450	69	11	(pregnant)

HOUSE DUST DESENSIBILIZATION

by

HELGE COLLDAHL

In a seri [illegible]
medical [illegible]
positive [illegible]
ent food stuffs in 31 per cent and to pollen in 19 per cent

Dust therefore is the antigen in the mentioned material that gives the highest percentage of positive skin reactions.

When patients with a positive skin test inhale the antigen, the provocation tests turned out positively in case of dust in 72 per cent, in case of pollen in 59 per cent and in case of animal dander in 20 per cent.

For two reasons, therefore, dust is an extremely important antigen for the troubles of asthmatic patients in Sweden. A positive skin test for dust is more often a sign of hypersensitivity of clinical importance than a positive skin test for other antigens

When using different dust extracts very different results were obtained both by skin testing and provocation tests.

The effect of hyposensitization is usually very good. Long-time treatment is essential. When a strong dust extract (measured by skin titration and provocation tests) can be prepared from the patient's home, the hyposensitization is carried out with this extract

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HOUSE DUST DESENSIBILIZATION

by

B SANCHEZ-CUENCA

[illegible]

sponding extracts. The number of patients studied both by myself and my collaborators in my private office, as well as in our Asthma Institute from the year 1945, amounts to 8420, among which 3640 were sensitive to dust. This figure represents 43.2 per cent of the total number of asthmatic patients up to this day. Of them, 1721 had treatment only of dust extract and 1919 were treated with the extract alternated with an auto-vaccine of the germ or germs cultured from the nasal secretion. In certain cases also from sputum.

As a rule, desensibilization proved effective and symptomatology gradually

receded when the doses of the allergenic active substance were increased. But the simultaneous use of a nasal auto-vaccine alternated with the dust extract proved even more effective. The useful action of the vaccine in these cases may be ascribed to the elimination of the nasal allergic episodes of bacterial etiology which add to those produced by dust, or perhaps because the infectious episodes are in favour of a pathogenetic action of the dust, increasing the permeability of the mucous [illegible]

asthma.

5 per cent of our respiratory allergic to dust patients showed resistance to desensibilization, disclosing their resistance in an increase of symptomatology after the extract injections. In these cases they have been applied a protective treatment of Cortisone and ACTH. While desensibilization went on and once a high dose of allergenic extract was reached, we gradually suppressed the protective pharmacology, at the same time reducing the extract doses down to a quantity which being effective, could be borne by the patient without any Cortisone

Taking into account the different allergenic richness of house dust, we have prepared 3 different types of extracts, convenient to the 3 groups in which we have divided our patients:

a) Rural or farms house dust, very rich in organic matter, mainly of animal origin

b) Marine or sea-side dust, especially rich in spores or fungi.

c) Town or large city house dust, generally rich in those factors giving a particular character to the two previous ones On a base of reactivity common to the three extracts, patients sensitive to dust, fluctuate in their reactions to them, according to their urban, rural or sea-side condition and we have taken advantage of these differences in their skin reactions to prescribe the corresponding extract treatment.

Specific desensibilization is necessarily long. After two years of applying the maximum dose (1 c c. of 4 per cent extract) we still continue giving a monthly injection of that dose for another year and even longer.

When desensilization is effective, the cutaneous activity diminishes, which shows in the disappearance of pseudopodes in the intradermic test; the hyperhemic halo also reduces but a round lump is still obtained which corresponds to a two crosses reaction. In fact, no real desensibilization is obtained, but a process of hyposensibilization showing a lighter reactivity both of the skin and of the shockorgan.

BACTERIAL VACCINE THERAPY*

by

A. W. FRANKLAND

There is considerable difference in opinion as to whether bacterial vaccines are of use in the infective type of asthma and whether any effect obtained is specific. An autogenous bacterial vaccine apparently will give good results to many patients A control trial was carried out to see whether bacterial vaccines give specific help to infective asthmatics. Patients were selected for the trial if the asthma was of a predominatingly infective type, and in whom a bacterial vaccine would be expected to be helpful. The vaccine was made from the organisms found from culture specimens of sputum or from a post nasal swab. The organisms that were considered significant were streptococcus viridans or a non-haemolytic streptococcus when in almost pure culture, any pneumococcus or haemophilus influenzae or Friedlander's bacillus Each patient received the best available standard method of treatment and in addition received a bacterial vaccine or a control fluid. Two doctors took part in the trial. One of them believed that an autogenous bacterial vaccine gave specific help, the other doctor believed that any help obtained was quite non-specific in effect and that saline would give as good results A statistician placed the patients either in the vaccine group or control group by means of random number tables. Each doctor reviewed his own cases for a year, but not until the end of the trial did he know whether the patient had received a bacterial vaccine or carbol saline control.

It was intended that each doctor should follow a hundred cases for one year. One doctor followed up 89 patients and the other 95 patients. A system of scoring was used for assessing the final overall result. There were frequently several types of organisms in one vaccine. A mixed stock vaccine was added to all the autogenous vaccines. The strength of the vaccine was such that it contained 10 million per ml. of each of the autogenous strains. The control fluid was 0.5 per cent carbol saline

It was found that 54 per cent and 62 per cent (average 58 per cent) improved on the vaccine, while 51 per cent and 54 per cent (average 52.5 per cent) improved on saline injections.

* (This article appeared more fully in the British Medical Journal (Oct 15, 1955, p. 941): *Autogenous bacterial vaccines in the treatment of asthma* by A W FRANKLAND, W. HOWARD HUGHES and R H GORRILL)

The trial showed that when an active interest is taken in an asthmatic patient, half the patients for a period of a year will obtain benefit. Any result reported that does not show a statistically significant improvement on a figure of 50 per cent relieved, does not support the value of any allegedly specific treatment. It may also be pointed out that *only under the conditions of the experiment* was it shown that there was no difference between an autogenous vaccine therapy and saline injections in the treatment of asthma. It may yet be shown that bacterial vaccines under other conditions, can give specific benefit in the treatment of asthma.

SUMMARY

A controlled trial was carried out in 200 cases of infective asthma. The patients were kept under observation for one year and given general supportive symptomatic treatment. It was found that regular injections of an autogenous bacterial vaccine produced no greater benefit to asthmatic patients than similar injections of carbol saline. Over 50 per cent obtained benefit from the treatment.

DISCUSSION

HELGE COLLDAHL

According to the results reported by Dr Frankland one cannot expect any result from bacterial vaccine treatment

We have administered both stock vaccines and auto-vaccines to patients whose asthma is worse in connection with infections and we are under the impression that asthmatic troubles after infections are sometimes shorter and not so severe when vaccine therapy is given.

In some few cases asthmatic troubles certainly become worse through vaccine treatment even if the doses are very small. I therefore think it is difficult in all cases to deny a more specific effect from vaccine therapy.

There is a group of patients who are dust sensitive but who rarely experience distress other than in connection with infections. I think in these cases the most essential procedure is to give the patients hyposensitization treatment with dust extracts in order more or less to eliminate the chronic irritation in the bronchi caused by the dust sensitivity In this way the resistance to infections probably becomes greater.

W. J. QUARLES VAN UFFORD

I was much impressed by the data supplied by Dr. Frankland, the more so, as I had a much better opinion of vaccine therapy.

The difficulty in evaluating a method of treatment in bronchial asthma is that in actual *treatment*, either of the attack itself or of the sequelae of attacks, we ask ourselves the question as to the point at which the drug to be administered will act, so that we will be able to determine whether, how rapidly, to what extent [illegible]

specific form of treatment such as pyretotherapy, sulphur therapy, gold therapy, etc., etc.

Dr. Frankland has succeeded in showing that autovaccine therapy is not a useful non-specific form of treatment and also that bacteria frequently play no or no [illegible]

doses of the vaccines might be administered at regular intervals of 5–14 days (therefore, this treatment is rather a method of maintaining immunity) — is combined with this form of treatment, increasingly large doses being administered at about the same intervals, and employed only in those cases in which it is definitely indicated.

We believe this treatment to be indicated in the following cases.

a) patients with bronchial asthma, subject to continuous attacks of bronchitis (increased ESR, large number of neutrophilic leucocytes in the sputum, an X-ray picture suggesting a large number of infections).

b) patients with bronchial asthma, showing a large number of focal infections, in whom there apparently is a relationship between the infections and the attacks of asthma

c) patients with bronchial asthma, liable to frequent attacks of dyspnoea following colds, bronchitis, etc. (this group often includes children).

d) patients with bronchial asthma, who do not show any intervals free of symptoms between attacks, but continue to cough, expectorate, etc We treat the secondary bronchitis in these cases.

e) patients with bronchial asthma, showing markedly positive skin tests for one or several bacterial allergens, whereas no definite focus (the possibility of a localization in the gall-bladder, tonsils or accessory sinuses of the nose being also borne in mind) could be detected.

f) patients with emphysema and recurrent bronchitis.

In preparing vaccines, preparation of the ordinary autovaccine is combined with that of a stock vaccine, the rule being that another vaccine is prepared when administration of the vaccine has failed to elicit any response or the condition of the patient remains unchanged after treatment has been continued for a few months. Bacteria from the patient himself and 'stock bacteria' are used in preparing the vaccine, which is composed in accordance with the positive skin tests

Extremely good results may be anticipated when these indications are observed. It should be borne in mind, however, that forms of asthma due to only one cause are hardly ever encountered The autovaccine will only be effective against the bacterial factor. To obtain adequate results, the other factors will often have to be treated as well.

B SANCHEZ-CUENCA

We believe to have at prese
asthma. Of our 8420 patien
treated, as basical therapy,
therapy, patients can be classified under four different groups:

a) with a *brilliant* result, corresponding to those whose sibilant symptoms remit after the first injections, paroxisms cease, expectoration disappears and the patient is for a long time in a position similar to normality and many times normal for the rest of his life, if the treatment has been long enough.

b) *good*, when the result of the vaccine shows in the evident remission of the symptomatology, in the disappearance of paroxisms, diminishing of bronchial

secretion, increase of their breathing capacity in repose but with persistency of a certain stage of dyspnoea, after an effort, disclosing the characteristics of an asthmatic dyspnoea even reaching the aspect of real asthma if the functional effort exceeds certain limits; the functional recovery of these patients can be estimated at 60 – 70 per cent. The disappearance of severe incidental catarrhs is a considerable advantage in their process

c) *middle*, with a slight symtomatic relief, hardly representing 10 – 20 per cent of recovery but with a fair reduction of serious bronchial attacks; this, anyway, implies a considerable subjective improvement.

d) *bad*, we include in this group those without any relief and also those getting worse after the vaccine therapy.

In our experience, the first group represents 15 per cent; the second group 45 per cent; the third group 30 per cent and 10 per cent the fourth group

In these grades, as a therapeutical answer, very important facts are the duration of the process, the existence of injuries to the bronchial wall, the tendency to broncho-pulmo sclerofibrosis, the concomitant circulation alterations and the undiscriminating humoral conditions on which a clear immunologic answer depends.

The composition of the vaccine may be very important to obtain better tolerance and the best useful effect The image in the culture plate which allows to evaluate [illegible]

prefered to make tests of the germs through an intradermic injection to the patient and observe the intensity of the reactions, but in the opposite way, that is, less quantity of those with a higher reaction and a larger quantity of those with a lighter reaction, but nevertheless taking into the composition of the vaccine all those under culture on the agar-blood plate We do not consider there is any *reasonable judgement on which to base the granting of any determined importance* to any kind of bacteria cultured from the breath exudes of the infective asthmatic. We have denominated the vaccines prepared in this way, 'compensated vaccines' because the reactionary activity is compensated in them with the mass of bacteria.

K. WILKEN-JENSEN

The results of Dr. Frankland and co-workers may be valid for adults but in my experience they are definitely wrong for children In the University hospital in Copenhagen we treat a lot of children with stock vaccine prepared from several hundreds of cultures from noses and throats of asthmatic children. We regard the prognosis for the children with what we call 'infection asthma' better than for the children with inhalation asthma The figures from my clinic show about 85 – 90 per cent of the asthmatic children symptomfree after a long-time treatment with the stock vaccine of the Danish State Serum Institute. Unfortunately I have no controls

FOOD ALLERGY

by

J. F. FARRERONS-CÓ

Not only are we ignorant, as yet, of the internal mechanism of allergic diseases, but the actual nature of the causes of allergy are also subject to considerable differences of opinion.

Some authors believe that the effect of domestic dust is the primary producer of respiratory allergy, while for others it is hardly, if at all, important. The latter authors stress the action of moulds To a third group, again, various kinds of food constitute the most important allergenic agents. And for yet another school of allergologists, bacteria are chiefly responsible for the existence of asthma.

This situation applies not only to our country but also to others. In the United States, for instance, we find Rackemann believing that most asthmas are infectious, but that food is not a factor of any importance. In that same country, on the other hand, Rowe declared that, in the majority of respiratory allergies, the inhalatory and alimentary allergens are involved in the same proportion, while bacteria have no effect

In France, Belgium, Holland, Britain, Italy and Spain, opinions are also very divided. For some authors, the cause of allergic diseases is bacterial infection; for others, bacteria have no particular interest, other causes being blamed

There are several reasons for this lack of agreement, viz.,

I. Lack of uniformity in diagnostic methods:

A. With respect to inhalatory allergies,

1) Authors favouring the intradermal reaction;
2) Authors favouring the dermal reaction;
3) Diagnosis based only on passive transmission.

B With respect to alimentary allergies:

1) Authors favouring the intradermal reactions,
2) Authors favouring the cutaneous reactions;
3) Authors favouring diagnoses with only special diets,
4) Authors favouring diagnoses based on pulsation hlanges and other procedures, e.g. the microprecipitation test, alimentary production of leukopenia, etc.

C. With respect to bacterial allergies:

1) Authors favouring the intradermal reaction,
   a) with extracts of whole bacteria;
   b) with polysaccharide fractions;

2) Authors rejecting all allergic tests with bacteria;
3) Authors favouring the Solis-Cohen test (bacterial cultures from the patient's own blood; cultures in infectious material from the same patient).

Yet another cutaneous reaction method, widely used in England, is the Prick method.

Another group of difficulties arises from the non-standardization of the extracts used in diagnosing:

1) aqueous extracts for the intradermal reaction determining their contents of nitrogenum;
2) water-glycerin extracts for the dermal reaction;
3) use of raw materials without extraction;
4) use of pure 'Endo' extracts (purified and concentrated extracts);
5) extracts determined by weight.

It is obvious that the same investigator using those different extracts in the same patient must get similar results.

I am at present making a survey of respiratory allergies with moulds (extracts of type 33 moulds); and to-day we are diagnosing many more mould-allergies than two years ago.

In France, Vallery-Radot and Halpern made a study of the problem of dust-allergy, which, having been fairly seldom diagnosed in that country some time ago, now shows an incidence similar to that of other countries.

A beginner in allergology, who bases his knowledge on the experience of others, will find his studies increasingly difficult owing to the variations in the way of life and food habits of the patients.

An author writing on allergy will, of course, relate his own experiences; and students searching for comprehensive knowledge are bound to go wrong if they attempt to copy exactly what they have learned from a foreign teacher, whose experiences cannot, of course, be completely relied upon in all circumstances.

Some time ago we had with us, in Madrid and Barcelona, Dr. Albert H. Rowe, doubtless one of the world's best allergists. In the latter town Dr. Rowe gave some lectures entitled *Clinical Aspects of Food Allergy*.

After listening to this scientist, whose views were extremely valuable to us (Rowe said that the problem of allergy was, generally speaking, a matter of food), the only conclusion we could come to was that neither dust nor bacteria had any considerable significance.

On the same day we listened to Dr. Rowe at the Faculty of Medicine at Barcelona, I received a folder containing some interesting words by Dr. Chobot, which I will copy here:

'... There are two currents of opinion with respect to food allergy. One, with its center in the West and Middle West, believes that food is

an important cause which, however, can only become intense in the cycles of higher respiratory infections. ... Another group, including myself'—continues Chobot—'believe that, although there exists food allergy, that does not mean that it can develop its activity during the cycles of respiratory infection; the important cause is the infection alone. I do not favour the theory of any increase of alimentary hypersensitivity during high respiratory infection; for my experience has taught me that alimentary hypersensitivity, when high respiratory infection is present, remains unchanged as long as the cause of shock is effective'.

In Cooke's work, Dr. Chobot, author of the chapter on Alimentary allergy, makes the following statements:

1) Contrary to what is generally believed, clinical alimentary allergies are infrequent.

2) Allergies following the eating of certain foods (after one hour) may be diagnosed by immediate testing. The patient generally knows the source of his allergy, and has no difficulty in talking about it.

3) Analysis of the delayed reaction is difficult, both by means of cutaneous tests and by provoked alimentary tests. As a rule, only the last reactions can be determined by therapeutic proof.

In his book on pediatric allergy, Chobot summarizes the causes of asthma on the basis of his experience with 209 children of under 3 years old. He finds that alimentary allergy (without inhalatory or bacterial allergy) was present in only 0.5 per cent of cases; 3 per cent had alimentary allergy mixed with a bacterial one, and 8 per cent had alimentary, bacterial, and inhalatory allergy combined. On the other hand, mixed bacterial and inhalatory allergy accounted for 48 per cent of cases.

As against this, Dr. Rowe showed a survey comparing the four greatest causes of allergy: the 1st, very frequent; the 2nd, less frequent; the 3rd, least frequent, and the 4th, infrequent. So far, he classes food as 1 in bronchial asthma; inhalatory causes also as 1; drugs and serums as 2, and infectious agents as 4. In the perennial type, he classes food as 2—still very important, therefore—; inhalants as 1 (most important), drugs and serums as 4, and bacteria also as 4 (i e. infrequent). Rowe's experiences in 1952, therefore, mean that alimentary causes are preeminent in allergy. These theories are supported by Vaughan, Rinkel and Randolph, but not by many other allergists, including Cooke, Feinberg, Rackemann and others.

Now let us suppose that both sides get the same therapeutic results, say, 70 per cent. Then Rowe's group may get this percentage by the most specific diagnostics. The second group may get the same result by using bacterial vaccines, whose specificity is doubtful, although the result is considerable. Both groups of investigators arrive at the same goal, but by different roads The Rowe group will eliminate the anaphy-

lectic shock, and produce alimentary micro-shocks. The Cooke group will attain that equilibrium by producing non-specific micro-shocks with bacterial vaccines.

It may be more suitable to the allergist to belong to the *latter group;* but none the less, Rowe's technique is the more reliable in the long run.

The effect of these techniques in our everyday work depends upon many factors. The patient's mental state; the time and patience which the allergist is able to devote to them; the realization of a mutual interest on the part of doctor and patient; all these and similar factors may make an important contribution. Failing this, the allergist may either join the other group, or prefer to adopt an eclectic attitude.

Diagnosis of Food Allergy

It is not easy to diagnose a food allergy, because of the slight validity of either cutaneous or intradermal tests; for, although they may appear to turn out positive, it may also be that the patient is not so sensitive to the food that produces a positive effect as for a food whose effect is negative. Therefore, a diet based on cutaneous experiment is unreliable. It is important for the allergist to know the order of frequency in which various foods provoke allergic attacks. In a small manual which I wrote I gave the five different statistics, including the order of frequency of the foods, and the types of food that would most quickly, and more slowly, provoke attacks. (Table 1). Naturally, such a table of foods is of considerable interest for the study of alimentary causes of allergic disease; and when a diet is drawn up, a knowledge of the table also provides a new order of sequence to follow in any alimentary additions, thereby avoiding fresh allergic troubles, which will aggravate the patient's feelings of depression and hopelessness. We must bear in mind that the patient pins his hopes on the doctor's knowledge and opinions, and rarely knows anything about the effects of food. Usually he has prejudices, such as attaching undue importance to colds, to defaecation or other organic movements; women, for instance, would feel troubled while menstruating; others, again, would worry about the weather, etc.

I will leave aside the various diagnostic procedures respecting allergenic foods, and confine myself to giving our experiences in our own country, Spain. First, there is the patient's clinical history to be written by the physician; including questions of work, habits, place and condition of the home, repugnance to any particular foods, frequency of their ingestion, etc. It is a common thing to discover a hypersensitivity on the part of a patient, of which he was completely unaware when talking about certain foods without a knowledge of any of them.

TABLE 1

wheat	43 %	cabbage	4.8 %	rye	2.4 %
milk	21.4 %	nut	4.7 %	dry grapes	2.4 %
chocolate	21 %	rapeseed	4.5 %	veal	2.3 %
eggs	21 %	banana	4.4 %	plums	2.1 %
kidney-beans	10 %	peas	4.2 %	radishes	2.1 %
tomato	10 %	peaches	4 %	garlic	2.1 %
fish	9.5 %	lamb	4 %	lemon	2.1 %
corn	7.6 %	apples	3.9 %	parsley	2 %
cauliflower	7.2 %	oats	3.8 %	shellfish	1.7 %
onion	7.2 %	asparagus	3.7 %	pepper	1.7 %
barley	6.4 %	artichokes	3.4 %	olives	1.5 %
rice	6 %	strawberries	3.2 %	oranges	1.2 %
celery	5.8 %	rabbit	3 %	herring	1.1 %
pork	5.4 %	carrots	3 %	chestnut	0 %
chicken	5.3 %	dry figs	2.8 %		
pears	5.2 %	beans	2.5 %		

As soon as this anamnesis is made—which generally informs us of an alimentary allergy, although it may not appear to be the actual morbific agent—the patient is put on a basic therapeutic diet, in order to attain an allergic equilibrium, and establish a level. For example:

Lunch: Milk of almonds
Rye bread
Apple marmalade.

Dinner and supper:
Rice-soup, made only of the meat of lamb
Toasted meat of lamb
Artichokes
Sweet potato
Grill
Lettuce
Olives
Pears and raw apples
Bread of almonds ('turron')
100 mg. B_2 and C vitamines daily.

This diet—followed by the patient for 2 weeks—is useful also to determine aetiologic developments from other causes. We do not mean that this diet will become completely non-allergenic; for sometimes patients will show a sensitivity to the meat of lamb, or to almonds, rice, etc.; but the diet is a useful auxiliary to diagnosis As I mentioned before it is necessary to get proper control of bacterial and inhalatory causes in order to obtain fruitful results from this diet.

In some cases the patient must be hospitalized in an air-conditioned ward (filtered air).

Having now established the allergenic equilibrium, we now add the presumable allergens, contained in so many important foods, e.g. wheat, milk and eggs. Allergenic diagnosis to these three foods is made by means of the alimentary provocations verified at, and before, the patient's own doctor's.

The proof of alimentary provocation takes place as follows: The patient arrives at the doctor's after a good night's rest, having neither smoked nor drunk, and on an empty stomach. The evening before, he has taken a simple supper such as we prescribed in the above diet.

At first the leukocytes will be counted twice while the patient is still fasting: the average has to be taken. After that the patient will take the food in question. If it is wheat, 3 or 4 spoonfuls of flour mixed with water, with a sufficient quantity of water and sugar added, and heated to a milk-like soup.

The proof with eggs consists in the ingestion of two boiled eggs, or some raw eggs. The milk-proof: drinking one glassfull is sufficient.

The pulse-rate must also be noted. This done, the food is taken, the leukocytes counted every 20 minutes until one hour after its ingestion. The pulse is taken again, and the number of eosinophils counted. Finally, the doctor must carefully observe, in the patient, the following reactions:

TABLE 2

1. sweat	9. stomach-ache	17. weeping
2. anxiety	10. weight on the stomach	18. nasal stoppage
3. restlessness	11. ardour	19. asthma
4. uneasiness	12. pain at the uterus	20. urticaria
5. palpitations	13. diarrhoea	21. erythema
6. sickness	14. colic	22. itching
7. dizziness	15. itching	23. dermal oedema
8. vomiting	16. sneezing	

The concurrence of a decrease in the number of leukocytes down to 1000, acceleration of the pulse, anxiety, restlessness and general malaise, etc. prove the unsuitability of the meal.

It is not difficult for the patient to diagnose himself at home, and find out, by the above method, which foods are prejudicial to him. The addition of the said foods must be in inverse order of sequence to that given in table 1.

With the above measures one may obtain a treatment that does not get entangled with the bacterial and the inhalatory one. My experience has taught me the necessity of intensifying our investigation of diagnostic

and therapeutic measures; thus, it may be possible to discover, for instance, that patients whose colds, before treatment, were extremely serious, suffer far less from colds after adequate treatment. Finally, some patients who come to us, diagnosed as bearers of infectious bronchitis, may resist attacks of asthma, thanks to the proper treatment for food allergy.

As Rackemann said: 'Not all that wheezes is allergy'. We may add: 'Not all that wheezes is bronchitis' — in the sense of 'classic' bronchitis of an inflammatory nature, and from a bacterial cause.

Indeed, we may also add: 'Neither does bronchial silence mean absence of bronchitis'. In short, although the symptomatology may appear absent on auscultation, we may find ourselves faced with a patient with silent bronchitis, who quite evidently requires treatment with adequate pharmacological measures.

ELIMINATION DIET

by

C. DE LIND VAN WIJNGAARDEN

Before dealing with my proper subject, I will set out briefly the considerations that govern my diagnoses of allergic diseases and the treatment of my patients. This also affords an opportunity to mention the names of those who were of great influence on my career, namely Professor Rudolf Magnus and professor W. Storm van Leeuwen, who both lectured at this University.

I am still grateful that my first schooling as Chief Assistant to Prof. Rudolf Magnus was a pharmacological one. Prof. Storm van Leeuwen was my tutor on the subject of allergy.

In his lectures on the treatment of diseases, Rudolf Magnus distinguished between several types of therapy, the main types being *symptomatic* and *causal* therapy.

The underlying principle of the causal therapy is: take away the cause of the diseases and you are cured. In the field of allergy pollinosis might be mentioned as an example of a disease curable by *causal* therapy.

In this connection we argue as follows. The cause of the pollinosis is the pollen of some plant or other. Prevent the pollen from getting into contact with the patient—in other words take away the cause—and the patient will be cured; that is: the symptoms disappear. This is —of course—theoretically possible; for instance, if one goes to sea, or, as was the custom in Germany, to Helgoland, during the flowering of the grasses. Another possibity is to arrange for the patient an allergen-free room, for instance an air-conditioned room—so that he can remain in his own milieu. In fact, however, this is no causal therapy, for though the pollen is one of the causes of the disease, the other cause is in the patient himself, namely in his hypersensitivity. So, this example had better be referred to as a case of *elimination* therapy.

It is even questionable whether causal therapy is possible. Certainly —it may be said—it is possible, if we make the patient insusceptible to pollen; i e. desensitize him. Theoretically this train of thought is correct, but it does not always hold in practice, as is evident from the quantities of antihistaminics taken in the pollinosis season. But even if the combination: *elimination* and *desensibilization* would work, the therapy is always of the *causal* type. For, the 'restitutio ad integrim' is not always reached. Also the duration of the disease plays a part.

We all know that pollinosis patients may finally develop hay-asthma and that these asthma-attacks may also occur at times when there are no more pollen in the air.

So in this case neither the elimination therapy, nor the desensibilization or the symptomatic therapy will cure the patient thoroughly. At best they may give some improvement because the yearly stimulus does not occur.

Finally also *psychic* factors will manifest themselves. It is conceivable that a singer suffering from pollinosis, feels herself threatened in her subsistence and that her mind gets fixed on this very point also outside the pollinosis season A generally known example is that of the man who gets pollinosis when he sees a painted rose. That also the hormonal effects are of importance appears from the fact that pollinosis usually occurs at the age of puberty and may be disappear at a later age.

Summarizing, it may be said that even in the rather simple case of pollinosis with a distinct cause of the disease, causal therapy is not easily possible.

I have purposely enlarged on pollinosis, because here is one specified allergen which could be eliminated.

In the case of pure asthma bronchiale things are different. It occurs only seldom that one distinct allergen can be designated as the cause. When somebody is hyper-sensitive to horses, the same therapy as for pollinosis will mutatis mutandis apply: remove the horse and the patient will recover. Usually the patient knows that he is hyper-sensitive to horses and in this case, the skin-test with horse—dander and hair—only serves to show that the patient is right.

In other cases, when the allergen, say a cat, is regularly present in the house, the patient does not always know that the cat is the cause of his asthma. One of my patients always got asthma, when he was staying in Amsterdam with his parents-in-law. In his own home he had never been troubled with it, but for some time he had. The cat-hair skin test was positive. On enquiry it appeared, that he had taken a kitten with him from the parental home in Amsterdam to his dwelling. When the cat had been removed, the patient was quite well again. So in this case the skin test was very valuable.

With most asthmatic patients things are, however, more difficult. If there should originally be one cause, it has often worked already so long, that even the elimination of the cause does not give recovery, because also other factors have come into play. Yet it may be expected that a great improvement may set in.

Thus it is often seen that if a person who is hyper-sensitive to house dust (which certainly applies to 90 per cent of the asthma-patients) stays in an allergen-free room—so removed from the cause— that

such a patient is freed from his asthmatic attacks as long as he remains in the room. When this is not the case, it should, of course, be ascertained, what the cause may be, and then it appears that it often lies in the *nutritional* field.

And now we come to the question how to find out whether a given food is the cause, or one of the causes, of an asthmatic condition.

The following points should here be taken into account:

1) There is a pure allergy for one specified food, which means that a minimum quantity gives a maximum reaction. In such cases the patient himself usually knows that his attacks are due to a specified food, and in this case the skin test only serves to prove that the patient is right. In other cases it may be ascertained by accurate anamnesis, whether a patient reacts to a specified food.

Last Saturday, for instance, I was consulted by a patient, in whose face an acute oedema manifested itself as soon as she tired herself when playing tennis. When I asked her some more questions, it appeared that since her early childhood, she had not been able to stand fish or eggs. Still this was not the cause of the present oedema, as she carefully avoided to take any foods containing fish or egg.

2) In other cases it can hardly be maintained that asthma manifesting itself after food has been taken is due to allergic causes. Many patients suffering from asthma feel oppressed after dinner. So there is a direct relation between dinner and oppression. As in the Netherlands the potato is the only regular ingredient in hot meals, while meat and vegetables being served in varying sorts, there would be every reason to think that these are cases of allergy to potatoes—the more so because there are no longer such feelings of oppression once the potato has been eliminated.

The result of the intracutaneous skin test, however, is negative in by far the majority of cases Moreover, there are no attacks of oppression after a dinner either, when the patient considerably reduces his potato ration. So this is contrary to the hyper-sensitivity to eggs, etc. already referred to, causing maximum reactions to minimum quantities.

Therefore the conclusion is that the quantity of potatoes eaten produces the attack of oppression quite mechanically, by obstructing the action of the diaphragma. The situation becomes worse when fat gravy is taken at the same time. For, indeed, this delays the emptying process of the stomach. Such mechanical irritation can also occur after cabbage, fat food and onions have been eaten. It is therefore always important that these patients should be given easily digestible food.

3) Further I wish to point to the fact that a certain combination of foodstuffs may cause an allergic reaction, whereas such a reaction is not caused by any of these foodstuffs separately.

Whenever it is considered desirable to find out whether there is any question of food-allergy in a certain case, skin tests and trial diets may serve the purpose, at least in everyday practice.

Skin tests (cutaneous- and intra-cutaneous): we always carry out a few skin tests, namely for egg, milk, beef, pork, fish and shrimps (i.e. animal proteins). They are often supplemented by skin tests for cheese, chocolate, potato, pulses and cabbage and by group reactions according to Bencard. Whether any more tests are carried out depends on individual circumstances.

For, indeed, there are serious drawbacks to such testing, especially where children are concerned. Children can indeed be subjected to a few tests, but if they have to be repeated, much psychic tension is the result. I have children skin tested by an assistant during my absence, so that when I come to see them later, they will not be frightened.

The matter is, indeed, different in the case of adults. They can stand many skin tests, provided such tests are carried out with the necessary care. I have done this for many years with various extracts, such of those of Brocopharm, Lifa, Bencard and Barford of Copenhagen, and in former days I also used the allergen-extracts of the Sächsische Serumwerke, which I have even tested for approval for many years.

Without pretending that I should not mind doing without the skin-tests, I must say that it is often hard to get a clear picture of their results. Of course I have seen amazing results in the course of the years (buckwheat, egg, milk, currants, spinach, cabbage, etc.), but in many cases the problem arises whether a skin test produces a positive or a negative reaction. Such doubtful cases make the job difficult. Moreover I have often found that someone reacting to the widest variety of foodstuffs did not recover to any appreciable extent when on a proper diet Such observations are in perfect *disagreement* with the device. *remove the cause and the patient is cured.*

When the investigation into the influence of the food on the asthmatic attacks of the patient is carried out according to this device, a complete recovery, or at least a marked improvement in the condition of the patient should follow when he is deprived of all food.

This brings us to the *diet-therapy*, which I am sure, you all know. My method is usually the following:

Starvation for one or two days;
then for two days rice boiled in water;
after this rice, vegetable, butter and sugar;
followed after two days by apple and apple sauce;
and finally one vegetable variety is added every two day.

So the *standard-diet* is as follows:

Morning: bread and vegetable butter and meat, sugar and apple, and tea as a drink.

Afternoon: same.

Evening: meat, rice, sauce of vegetable butter, vegetable (one variety) and apple.

This standard diet can be continued for a long time and is subject to variations. It is necessary for the patient to write down his daily diet and daily experiences in his food-diary. When the patient thinks he gets oppressed after eating a certain food, this test should be repeated at least twice. Different weekdays should be chosen, i.e. Monday, Wednesday and Friday and changes in the diet, should never fall in the weekend. The weekend breaks the normal rythm of life (weekend asthma).

Though I think that this is the best method for detecting the food-allergen, the disadvantage of the building-up diet is that it is hard to practise in boarding-houses. Also in many households it makes high demands on the housewife. Therefore, as is generally known, it may be useful to give an elimination diet by which one food or one group of foods is eliminated. In my practice, I act as follows:

First for four weeks a perfectly *dairy-free* and *egg-free* diet, even when the skin reactions to egg and milk are negative. Also here the diet should be carefully noted down and it should be emphasized that butter-milk and yoghurt and cheese are also milk-products.

When there is no clear recovery after a milk- and egg-free diet, we change over to a *meat-free* diet and then to a *carbo-hydrate-free* diet.

Vegetables may be eliminated group by group. In this way it may finally be found whether a certain food should be considered a harmful allergen.

What value should now be attached to the diet in the case of asthma patients?

During my twenty five years of practice as an allergologist, and, in fact, during several more years, in which I have been in close contact with the asthmatic clinical picture, I found that the number of food-allergens, as the only clear cause of asthma in adults, is very small compared to the large number of asthma-patients for whom house dust is the harmful allergen, mostly based on chronic bronchitis started in early childhood and on somato psychical influences. This does not mean that I do not prescribe diets to my patients. Of course, asthma-patients should only eat easily-digestible food, while for too heavy patients a reducing diet is indispensable.

DISCUSSION

R. ALEMANY-VALL

We have seen, in general, asthma associated with cutaneous lesions forming papules and eczemas or spots and prutitus of diffuse localization in which there were almost always small associated lesions of urticaria-form type responding quickly to an anti-allergic general alimentary regime (without bread of wheat, milk, eggs etc)

In other patients there were only cutaneous lesions to be found

In children with intolerance of, or allergic regarding food, exanthemas appeared over the whole body, except, generally, on the cheeks Some of these children suffered from intensive and improductive initial cough, sometimes even aphony to such a point that tracheotomies had to be practised. In the same children, this obstructive-laryngeal picture was repeated afterward and responded to an injection of adrenalin. In these children the same regime gave good results; the asthma had disappeared, whereas it was present continually on account of the immoderate consumption of harmful food.

We determine this general anti-allergic regime on the basis of foodstuffs containing small quantities of proteins, such as cabbages, egg-plants, carrots, artichokes, beets, chestnuts, Brussels-sprouts, vegetal milk, amino-acids, vitamins, chicken or lamb, jams, cooked fruit, olive oil and sobee.

This regime was, generally, sufficient; when it was not, we eliminated the suspected foodstuffs (comparing the alimentary regime every day with the conditions of the lesions) and added others; it was then a matter of much longer time to get good results.

We made a few times Rinkel's tests for stimulating to action disturbance and have also taken a leucocyte count, obtaining thereby some good results.

J. DUCHAINE

In my experience, the use of a standardized diet encounters a great many obstacles. And among these, the most important are certainly the dietary habits of the people, habits which can completely differ from one country to another.

For instance, in Belgium, where wheat and potatoes are the two basic foods, it is impossible to keep the patient strictly on a diet without cereals. The best way of getting around these difficulties is to prescribe a diet which is palatable [illegible]

chocolate. A few drops of tinned milk (i.e. milk that has been heated at a high temperature) are allowed and so are leafy vegetables and salads.

If no striking results are obtained with this diet within 10 to 15 days, the problem is reconsidered and some foods, likely to be clinically significant like potatoes, are struck out; others are permitted according, if possible, to the personal tastes of the patient.

ALBERT ROWE

The confirmation by Dr. Farrerons-Có of the value of my elimination diets is very important. Similar reports by allergists in other countries will be of great value.

Our constant use of these diets for 30 years has indicated about equal importance of food and inhalant allergy with a minimum of infectant allergy in bronchial asthma. Published statistics on nearly 3000 cases indicates food as the sole cause in 20 to 40 per cent in infants and young children, 20 per cent in the young or midaged and 20—40 per cent in old age. Food is often associated with inhalant allergy and inhalants alone cause about 20—40 per cent Drug allergy especially to aspirin must be remembered.

This frequency of food allergy is greater than usually reported, due in our opinion to several reasons.

1) Errors and fallibility in skintesting are most important. We test patients with 50 or more indicated foods by the scratch or puncture method.

fails. Intradermal tests nearly always give false or questionable reactions in addition to those with the scratch test and are not done. The clinical value of any reaction must be determined by injection-tests but only in the symptomfree patient which may take 4—12 weeks with the proper diet.

2) Because of this fallibility in skintesting our elimination diets excluding

diets as published with synthetic vitamins maintain the nutrition for long periods.

4) If the diet is proper and foods are the sole cause improvement at times moderate will be noted in 1 to 2 weeks It should be continued with 100 per cent

1 to 2 times

as in nort

more freq

eliminated foods. Minimal diets thus may be utilized even one with lamb or beef tapioc cooked with sugar and caramel, sugar up to 80 grams a day, salt water

and synthetic vitamins. With definite relief foods one every 3—5 days are added excluding those which reproduce symptoms. Enough of these foods must be eaten to maintain weight.

5) Our long recognition of exaggeration of food-allergy in the winter months also often causing recurrent colds and coughs with no asthma and improvement of food allergy in dry inland or heigh areas must be remembered.

Finally the classical history of bronchial asthma due to food allergy, especially in young childhood is restored. It was recently republished in *Progress in Allergy*, edited by Kallos in 1952 in an article on bronchial asthma due to food allergy in which my elimination diets and other advised treatment are also included. Regular attacks occur usually preceded with nasal symptoms suggesting infection but due to food allergy.

Temporary exhaustion of reacting bodies explains interim relief though allergenic foods are eaten daily. During summers, slight symptoms may allow liberalized diets. The strict cereal free elimination diet usually is again necessary in the autumn until late spring. Fever with vomiting due to food allergy may occur. Similar symptoms with above relief occur in adults and old age, though asthma *usually is more persistant.*

Food allergy therefore must be studied when recurrent or persistant asthma occurs usually exaggerated in autumn to late spring A diethistory of food-dislikes or disagreements and seasonal and geographic variations suggest foods If large scratch-reactions or a suggestive history to specific foods occurs their elemination may give relief. Usually skin-reactions are alient or questionable, justifying our cereal free elimination diet. Inhalant or rare infectant allergies always must be remembered. Along with control of food and inhalant allergies, symptomatic *relief with usual drugs but never opiate, demoral or sedatives*, and if necessary cortisone and ACTH is indicated. These can be reduced or excluded as the brochonazal symptoms gradually are relieved with anti-allergic therapy.

With the free use of elemination diets, the importance of food allergy in bronchonasal and other manifestations of clinical allergy will become evident As with any other diet or test, elimination diets must be used for more than a few months and on more than a few patients to attain necessary experience and facility in their use.

BRONCHIAL ASTHMA - ASPECIFIC THERAPY

by

FRED W. WITTICH

A large proportion of cases of bronchial asthma have an existing hypersensitiveness of the bronchial mucosa or musculature in which the latter structures react to a variety of stimuli, such as cold, wind, dust, excitement, and fatigue.[11] This condition of hypersensitiveness should be regarded as a pathergy rather than an allergy.

In the broad sense, aspecific treatment of the patient with bronchial asthma consists of those nonallergic measures which correct the abnormal alterations in physiology. This would include all symptomatic treatment, such as drugs and operative procedures.

Therefore, with all methods of specific and symptomatic adjuncts, as discussed at this symposium, the writer's paper will deal exclusively with these aspecific agents which have been considered as conferring some degree of immunity in an indirect manner.

The employment of such aspecific measures without first determining and adjusting specific etiologic factors, as much as is practical and possible, is inexcusable.

At the present time, the increasing improvement of our diagnostic procedures warrants the abandonment of aspecific measures formerly proposed when we were groping for some beneficial remedy which would be a shortcut to proper immunologic methods, and when the proper approach to diagnostic procedures for many reasons were markedly limited. A comparatively few aspecific measures in the present day therapy of asthma are warranted.

There are, however, frequent occasions when specific and symptomatic measures must be complemented in order to give the patient some comfort and relief. At the onset and for some time, there may be difficulty in determining the specific causes of symptoms and, when known, they, as well as the complicating changes, may offer considerable difficulty to manage.

Aspecific measures which have been used with some relief to the patient with bronchial asthma include tuberculin; nonspecific proteins, such as milk and peptones, and shock therapy; artificial fever; colloidal sulfur, the use of endocrines, particularly ACTH and cortisone; vitamin preparations; physiotherapy; psychotherapy; roentgen-ray therapy; bronchoscopy and iodized oil; surgical procedures; digestant chemicals and enzymes; corrective fluid and electrolyte metabolism; urinary

proteose; ionized air, et cetera. All of these methods have their advocates, but time and trial have eliminated a number of them as valueless. A few of the most important will be mentioned.

Surgical Procedures. Any surgical methods to inhibit the autonomic nervous system's influence on asthma have been mainly 'partial and temporary'.[3] Such procedures may cause various annoying complicating nervous phenomena. 'Stellectomy' after estimation of a blocking anesthetic agent seems to be the method of choice. Other procedures, such as unilateral extirpation of the cervical sympathetic ganglia, vagus section, and resection of the posterior pulmonary plexus, by and large have been disappointing.

Digestant Chemicals and Enzymes. These have been used for aiding food digestion. It is well known that gastrointestinal disturbances may be a precipitating factor of asthma. Nitrohydrochloric acid or urea nitrate may favourably influence these factors. Citric acid[2] in 4--16 cc doses of a 25 per cent solution in water, or lemonade, sipped with the meals may be tried The digestive enzymes, pepsin and pancreatin, are helpful Coated tablets of Cotazym (Organon) are preferred where digestive disturbances are present, as they do not contain bile salts which act as a laxative

Fluid and Electrolyte Metabolism. In 1940 Stoesser and Cooke,[9,10] reported the importance of electrolyte and water exchange in bronchial asthma. Sheldon[8] and his associates reported cases where asthma could be induced or aborted at will when observed in regard to water and sodium metabolism, regardless of whether they were initiated by foods or by inhalant allergens. They noted the asthma attacks were associated with considerable loss of body fluid and increase in the urinary sodium, and that the loss of sodium through the urine in direct relation to the body water loss. Harsh and Donovan[4] observed the effect of the wide variation in potassium and sodium intake in children with asthma. Their observations, which were carefully controlled by ingestion experiments, demonstrated that a high sodium intake increased the amount of asthma, whereas high potassium intake had little or no effect. Experiments now being carried on by the author in collaboration with others indicate that besides the sodium and potassium metabolism to be considered in allergies there is also that of calcium and other electrolytes.

Urbach and Willheim[12] made chemical studies of a similar nature when endeavoring to ascertain the allergic action of certain organic acids. They showed that the symptoms were the result of anions. They emphasized the importance of experimental testing in these cases, since patients are also known to be allergic to a number of cations It must be kept in mind that foods containing acids, such as vinegar or acetic acid, may produce allergic symptoms, or even the acid in sour apples

may be a factor (wine, oranges, lemons, pickles, et cetera). Negative skin tests to these foods when shown to produce symptoms by ingestion may be the result of the acid or alkalines contained therein.

Heretofore observations of electrolytes in the treatment of allergic states have been on sodium restriction and increased potassium intake. The author's experiments in collaboration with Dr. Irvin Moore have shown that electrolyte abnormalities are found in those allergic patients where there is more or less prolonged dehydration due to lack of fluid intake, or loss of fluids as in the profusely 'weeping' eczemas, particularly in children, and which is frequently complicated by water loss due to diarrhea.

In angioedema, during the swelling as a result of escape of fluid into the perivascular or extracellular compartment, there is a loss of K. Even between attacks the serum Na values in mEq is a maximum normal or slightly above, while the K is usually the minimum normal or less. During the attacks there is a definite K depletion.

In severe, acute, and generalized infantile eczema with weeping, particularly if associated with diarrhoea, there is a considerable loss of potassium. Following a low blood potassium level in these cases, either Butler's, Darrow's, or Baxter's Electrolyte Solution No. 2 should be given intravenously. This may be lifesaving and result in restoration of the skin from an irreversible condition under other anti-allergic measures alone.

Patients suffering from exfoliative dermatitis with marked edema of the subcutaneous tissues and exudation lose electrolytes through fluid loss, and K is frequently found low in these patients A repair solution containing potassium and calcium should be used in these cases.

In status asthmaticus or severe intractable asthma the patient is usually dehydrated from lack of intake of fluids by mouth. Sweating increases this dehydration Hydration is customary by intravenous introduction of 5 per cent glucose in normal saline or distilled water. There is no advantage in using larger concentrations of glucose particularly when the patient is receiving ACTH or cortisone. A potassium deficiency in these patients may seriously disturb the Na/K ratio. Calcium which diminishes capillary permeability should be increased more than that contained in the present repair solutions. Chloride values are usually found slightly in excess in severe asthmas and angioedema and should be at a minimum. Morphologic changes in magnesium deficiency include increased vascular permeability, myocardial fibrosis, neurologic degenerative changes, and the nephrotic syndrome. Like potassium, magnesium is mainly an intracellular substance. The serum concentration is quite low, 1.4 to 2.5 mEq/L. Due to hemoconcentration seen in severe dehydration, as in severe bronchial asthma, there is a comparatively high

serum magnesium. Serum levels above 6 mEq/L are associated with progressive depression of cardiac conduction and neuromuscular activity, which is to be avoided in severe bronchial asthma with myocardial damage. The serum level of magnesium should, therefore, be comparatively low. Repair solutions more suitable are proposed for these cases as follows: Travert 10 per cent Electrolyte No 2, Darrow's Solution and Butler's Solution have been used successfully. Aminophylline and epinephrine can be added to these repair solutions

Ethylhydrocupreine has been used in asthma with favourable results.

Alcohol When aminophylline fails to give relief, Brown[1] recommends the intravenous administration of ethyl alcohol 5 per cent, in glucose saline. To the alcohol solution 0.10 to 0 50 ml of 1 : 1000 epinephrine should be used. The drip is regulated to 80 to 120 drops per minute until the patient shows a pink flush or mild excitement. *When the patient falls asleep, the rate of injection is reduced to 60 to* 80 drops per minute. The procedure requires about two hours.

Urinary Proteose. In the past there has been much discussion of urinary proteose, with some advocates. Time has shown this substance to be of little value and the results are comparable to those of peptone injections.

Ionized Air Inhalations. These were tried by Landsman[5] to counteract the effect of weather changes on the asthmatic patient, and were claimed to show a high incidence of improvement.

Roentgen Therapy. This has been used more in the past than it is at present. It should be applied only by the roentgenologist who is familiar with its technique. The author has seen cases in which patients with progressive intrinsic asthma obtained considerable relief for some time from roentgen therapy when all other measures failed to help. The advent of ACTH and cortisone in this type of patient has practically supplanted other methods of treatment.

Artificial Fever Therapy. The use of remissive therapy, or treatment aimed at producing a prolonged symptom-free interval, particularly in patients who have received cortisone and ACTH for long periods with decreasing effectiveness, or where side reactions develop from the use of these hormones, should be considered. Frequently the use of artificial fever is the most effective method of inducing a remission Typhoid [illegible]

or higher has been produced, is helpful.

Another effective fever-producing agent is Piromen[R] (Travenol), a

* Kirk Manufacturing Company, New York, N Y. This contains no Paratyphoid A or B organisms which may cause shock

sterile, nonprotein and nonantigenic bacterial polysaccharide in a stable, aqueous, colloidal dispersion for parenteral use. The product is marketed in a bottle containing 10 gamma per cc. The initial dose intravenously is 0.05 cc (0.5 gamma), which is increased until an adequate fever response is induced.

Physiologically Directed Therapy. Various adjunctive physiotherapy procedures have been advocated in the treatment of asthma. Diathermy may be of temporary benefit where heat and sweating are helpful. Treating children with ultraviolet rays may be beneficial by improving the general health.

Measures Used to Aid in Restoration of Impaired Function (in patients with status asthmaticus and those with severe protracted bronchospasm). These procedures vary with the individual patient, and may consist of intermittent or continuous oxygen inhalations Thirty to 50 per cent oxygen may be given by oxygen tent, double bent tube, or nasal catheter to relieve anoxia and functional pulmonary emphysema. Intermittent administration of the same strengths of oxygen are safer where there is considerable advanced emphysema.

Helium-oxygen inhalation in the proportion of 80 per cent helium to 20 per cent oxygen is used to aid alveolar ventilation, but the studies of Schiller et al [7] failed 'to show any clear-cut difference between air and a mixture of 80 per cent helium and 20 per cent oxygen'. In eight severely ill patients these authors observed no significant change in the expiratory reserve volume, the inspiratory capacity, the vital capacity, or the speed of flow during the measurement of vital capacity.

Intermittent or continuous pressure is used to increase the diameter of the bronchi and maintain adequate ventilation. It may be used also in pulmonary edema. Intermittent pressure breathing is also used with negative pressure in expiration. By this means mucous plugs may be eliminated where coughing was ineffective.

These procedures may be accompanied by the continuous use of nebulizing or bronchodilator solutions, singly or in combinations, of which there are several on the market.

Iodides have a nonspecific action by preventing the mucus from becoming dry and adherent to the bronchial wall.

Patients refractory to epinephrine and aminophylline get considerable relief by the administration of 50 mgm. of Demerol[R] intramuscularly every six hours for three or four days only Dilaudid subcutaneously in 1 mg doses every six or eight hours for three or four days may relieve a protracted bronchospasm. Both narcotics are habit-forming and should be used only where the usual bronchodilators fail.

Bronchoscopy is used frequently as a diagnostic procedure in asthma and simulating conditions. The removal of inspissated sputum by means

of the bronchoscope may relieve a status asthmaticus. The discomforts and damages from the use of iodized oil in connection with the bronchoscope exclude its possible benefits.

Prickman and Moersch[6] point out that bronchostenosis frequently results in asthma resulting from inflammatory changes. This narrowing of the lumen retards the flow of air and contributes to the retention of secretions. Subsequent extensive observations by Moersch and his co-workers continue to substantiate the value of bronchoscopy in selected cases.

The subjects of physicotherapy, the treatment of emphysema, and psychotherapy as aspecific measures are omitted in this discussion because they will be presented by able authorities participating in this program to morrow.

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DISCUSSION

R. ALEMANY-VALL

We can consider as desensitizing treatments:

1) Vitamin A in massive doses administered orally and taken at regular intervalls; by itself, it will cause the disappearance of coryzas of non-specific allergic type;

2) Gamma-globuline injections which produce perhaps an earlier effect in rhinitis, also;

3) Azo-proteic histamine in cases of nasal colds the origin of which is unknown, and in which there is a principal or secundary physical factor. They contribute for instance, to the action of the microbial vaccines;

4) Thyreoidin in medium or large doses, lowers the sensitivity to colds and therefore, to catarrhs, in certain patients of normal appearance;

5) Pyromen (hydrocarbonated portion of certain pneumococci), not administered *intravenously, which is generally not tolerated, but sub-cutaneously* in sufficiently regular injections for infections type rhinitis and asthma;

6) Pregnandiol extracted from the urine of the patients by Aswood-Jones procedure. Intradermic injections every 3–5 days, without taking into account the epoch of intermenstrual period, specially in crises asthmatiques of premenstrual appearance.

We think, that the effect, although specific to a certain extent, is really non-specific, similar to that of azo-proteic histamine acting upon the premenstrual tension, of primordial histaminic influence,

7) The premenstrual serum of the patient produces sometimes good results; we have even seen two cases of premenstrual facial eczema treated with folliculin with good results;

8) Nitrogenized mustards in small doses, only three injections on alternate days, their action being similar to that of ACTH; they are not dangerous in such small doses It is sometimes necessary to administer antibiotics before and after the treatment,

9) Tuberculin or similar products which, although they may act non-specifically, usually produce good effects, at least at the beginning of the cure in those asthma cases, in which a small pulmonar fibrosis is present, and they act afterward as specific agents.

E. WOLFER-BIANCHI

It would not be right, not to mention the use of Iodine-Pepton in the non-specific desenzitation in the treatment of asthma.

I remember the names of Auld and Pollitzer, using Pepton alone with intramuscular injections, and Cantonnet, using a certain preparation of Iodine-Pepton, *which he calls Desensibilisine. I use myself since 20 years the Iodine-Pepton* of the french pharmacopoe with intramuscular injections every 5–7 days, beginning with a dilution of 1 : 5, and increasing the dosage. I can assure you, that a great part of asthmatic patients react very well and that the curative effect is a highly good one.

THERAPY BY HOME- AND FAMILY-EDUCATION

by

ZAIDA ERIKSSON-LIHR

The outstanding advances of recent medicine are of great value to the allergologist of to-day in determining what stress it is that has changed the reaction of a normal person or a person with a latent allergy to manifest allergy, (Fig. 1). The specific sensitivity can be defined through skin and provocation tests. The focal site of infections causing an allergy is nowadays not too difficult to localize. The determination of functional sufficiency or insufficiency of the hormones still render us some difficulties, which seem however easier to solve day by day, thanks to the new methods of hormone titration. Last but not least, in medicine to-day the ever increasing understanding of the psychic stress as a cause of allergy is well worth mentioning.

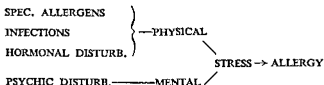


Fig 1

The means of combating the pathological processes found in the allergic organism are also greatly improved. I only like to mention specific and unspecific desensitizing, the elimination of focal infections, new and effective antibiotics and the long row of excellent hormones. Accordingly the allergologist can with a great deal more confidence than before terminate the patient's hospitalization and transfer him to homecare. But at this point the physician soon enough observes that new difficulties arise. The patient, who quickly recovered in the hospital, often at home soon developes new symptoms and has to return for treatment.

Yet the doctor had scrupulously tried to unravel the case, had questioned the patient on his home- and working-conditions, and warned him of the specific allergens he should avoid. He even had as a parting gift pressed into his hand a pamphlet explaining causes and cures for his allergy. As a result the patient, who is allergic to horsehair, conscientiously avoids visiting the stables, but unfortunately sleeps every

night on a horsehair mattress, which causes him asthma attacks. The patient, who is allergic to cowshair and sheepswool thoroughly avoids these animals, but at home during the day walks on a rug woven with cowshair and sleeps in a bed next to a woolen wall rug. Another patient lives in a damp house by the sea with mold growing under the wall-papers and in the cracks in the floor and even in her pillow which she has neglected to clean.

The allergologist sacrifices much time and work in examining his patient and treating him. But how often has all this work been in vain? The patient has not understood the doctor, has not been able to co-operate, has forgotten. We write pamphlets and have them printed to enlighten the patient and his family. Such pamphlets are already available in every country where there is advanced allergy work. But a pamphlet quickly becomes out-of-date. Let us remember all the new chemical substances which are used every day in hosiery and clothing, in materials, foods, medicines, and in the different industries, and we realize that such a pamphlet can stay up-to-date only for a certain time. If such a great change in substances did not occur practically every day, I would suggest to the International Association of Allergologists to nominate a committee to draw up these pamphlets and to distribute them in millions all over the world. Unfortunately this is not possible—each country must have its own pamphlets which are in accordance to the life and habits of its population. Such a pamphlet is of considerable help.

What else can be done to educate the allergic patient and his family? Patients' Clubs are of great importance. The patients receive psychological satisfaction in being able to discuss with one another the nature of their sufferings and distresses. They want to feel that they are worthy of consideration and do not want to be forsaken or misunderstood as allergic patients often are Short lectures on allergy with following discussions are very much enjoyed in these meetings in which also the patients' family eagerly partake, because of their wish to learn to understand their suffering relatives. These lectures can be held by doctors, nurses and also by the patients themselves. Such meetings of the allergy patients' club in Helsinki gather thousands of interested and grateful patients and their relatives and seem to be a great event both from the educational and social point of view.

An educational program on allergy must be out-lined by someone who has time and interest enough to devote to it. This person must also be trained to keep both ears and eyes open for everything new that happens in the field of allergy. This is not an easy task. I would like to mention that recently we were consulted on numerous current cases of hives, eczema and asthma for which it was difficult to find a cause. Finally it was discovered that the underlying cause was the new winter

turnip rape plant (Brassica Rapa Oleifera), which was recently started to cultivate in our country and the oil of which is used in cooking, salad dressings, mayonnaise, etc. and specially in the production of margarine. This Spring a great many men complained of itching and eczema caused by their new clothes. It was established that this was due to a new quality of unbleached tricolette underclothing, in which the cotton seed residuum caused allergy. The same reason for allergy was noticed in cases where the patient used unbleached bed-linen. One of the severest allergies is sensitiveness to asperin, which may cause asthma, constitutional shock, even death. Regardless of our constant warnings to patients of the great danger in using asperin, unexpected states of shock were evidenced. Investigations brought forth that headache powders contained under a different name a substance related to asperin All these facts must be registered in an *allergy black-book*, which serves the doctors as a warner and the patients as an educator. But who has the time and the energy to collect all this data? The practicing allergologist does not have time for it. Besides this work requires a person who is familiar with the different details of the homes and their surroundings and who is able to complete this knowledge with studies of the new materials modern industry has brought to our homes and our working places, especially in foods, medicines, cleaning agents, paints, and those used in home decorating.

In Helsinki at the Hospital for Allergic Diseases—a hospital specialized in the treatment of all different allergies and which at present has only 40 beds, but an out-patient department which during last year had 16,500 visits—we have trained for this purpose a special personnel to aid the doctors. These allergy nurses, who have a training of a Social nurse and know all about case-work, not only keep their eyes open for new allergens, but also personally study each new hospital case as a help to the doctor.

When a patient is admitted to the hospital, the allergy nurse fills in a special 'home'-page of the patient's case-history. The patient is requested to give as accurate a description of his home conditions as possible: the number and size of the rooms, the number of family members who live in these rooms, also the age of the family members, what type of bed do they have, the filling of mattresses and pillows, is furniture new or old, upholstered or not, what rugs there are on the floors, what pets or farm animals, what flowers, what working-conditions, etc. This information gives the physician a good background for his studies and allows him to compare the history with the results obtained from skin testing and other examinations. If we deal with a child, a thorough inquiry is made into the earliest childhood and its diseases. In women the menarche and climacterium are investigated, thus giving a

basis for hormonal studies. During the patient's hospitalization the allergy nurse pays daily attention to the patient, discusses further with him the home-, working and economical conditions and becomes thus acquainted with the patient and his personal physical and psychic stress.

It seems easier for the patient to open his heart and tell his manifold troubles to the allergy nurse than to the doctor. After the examination and the treatment of the patient is completed and the doctor has done his utmost to give the patient the necessary medications and advice for home-care, the patient is referred back to the allergy nurse, who has won the patient's confidence. The allergy nurse goes once more through the case-history, compares known home facts to results obtained from examinations and endeavors to make a further dive into the environmental situation of the patient. She explains about materials containing wool, feathers and different animal hair, she advises the patient how to avoid dust in the home, she names foods to be avoided and so on. When discharged from the hospital the patient is requested to report to the allergy nurse once a month and more often in case his health has not improved. The nurse then discusses the situation with the treating physician, keeps in contact with the patient and calls him back when necessary.

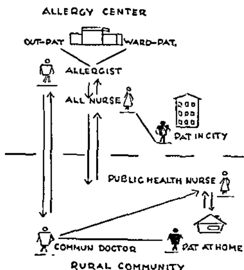


Fig 2

Finland is very fortunate to have a governmental Public Health Nursing system developed throughout the whole country. In every rural community there is for the community doctor's assistance a Public Health Center with a Public Health nurse and a mid-wife to every 4000 inhabitants. If our patients are from the city of Helsinki and their homes are visited by the allergy nurses, they are referred back to the out-patient department of the Allergy Hospital if needed. In case the patient living outside the Capital needs personal care or a visit to the home, he is advised to turn to his community doctor or Public Health nurse, who are in contact with the allergy nurse and the physicians at the Hospital for Allergic Diseases. (Fig. 2). In this way we have developed a system for home education, study and care for the

allergic patient and which system seems to us to be of utmost importance. Thousands of letters circulate yearly between the hospital and the patients. They save the patient useless calls to the doctor, but promote them when they are really needed. These letters combined with necessary general pamphlets provide the patient allround home education on allergy and make him and his family familiar with his personal type of disease. It also allows the hospital a follow-up of the patient, which seems to be of great value.

SUMMARY

In the social department of the Hospital for Allergic Diseases in Helsinki, Finland, specially trained s.c. Allergy nurses keep track of the development of the general allergen situation of the country. Through personal contact with the patients in the hospital, correspondence with them and visits to their homes after discharge from the hospital as well as through contact with Public Health nurses and doctors throughout the country, the Allergy nurses are able to provide a special home and family education of great importance. This is supplemented with written pamphlets and meetings of patients and their family members at which further educational programs are developed.

DISCUSSION

B. STOKVIS AND A. J. WELMAN

It is evident, both from the literature and from our own experiences, that a large number of patients with psychosomatic affections passed their youth in disharmonious families. This circumstance is of consequential importance for the treatment of patients with bronchial asthma, for which reason we shall briefly examine the factor family-relationships.

A family may be regarded as a structure of mutual relations among several persons living together. We may consider the family as a psychological unit, in which, therefore, no component elements should be studied separately. The affective interaction between the members of the family is to a large extant determined by the family-bond A closer study of this family-bond enables one to differentiate between a normal and an abnormal family.

The emotional relationship between different individuals may be based either on an *attachment*- or on a *binding*-relationship The mentally healthy person feels 'bound' to his fellows, he is able to meet the other person by a surrender of self, he is capable of giving love The neurotic family, on the contrary, is characterised by a relationship based on *attachment* An individual, who, owing to disturbances in his mental development (e g. through wrong education), has remained stuck in this attachment-relationship with his milieu, will retain an infantile-erotic attachment to it. He is capable only of feelings of dependence and can only receive love For a child, attachment is the normal emotional relationship When adults are incapable of forming a bond with others, and relations based on dependence remain prominent, the family life is pathological. These feelings of dependence obstruct the individual development of the members of [illegible]

adult life.

Within the family, the members exercise a mutually educative—and/or re-educative-influence on one another. The family as educative milieu depends, inter alia, on

1) The personality structure of the members (temperament[1]);
2) The mutual relation between the parents (unconscious drives);
3) The parents' sence of responsibility towards the children.

[illegible]

ship with them In many cases the parents themselves have remained stuck in their own infantile-erotic feelings of attachment, they are incapable of giving love either to each other or to their children, and strive only after the satisfaction of their own desires To this end they utilize the child, with the consequences that may be expected

From the psycho-hygienic viewpoint the most important cause of a disturbed family-life must be sought in the parents. Since it is completely impossible to prevent neurotics from getting married, disturbances in family will always tend to occur. They are, in fact, the more likely because, (in accordance with the genotropic theory of Szondi) there appears to exist a strongly attractive force between neurotic individuals.

The question may now be asked to what extent a disturbed family-bond may also manifest itself in a psychosomatic affection. With regard to bronchial asthma, Alexander already pointed to the occurrence of 'frustrations' during infancy. From the biographic anamneses of patients with bronchial asthma examined in the Leyden Psychosomatic Centre, it appears that nearly 80 per cent had had a disturbed family relationship. The psycho-diagnostic examination of these patients showed that they are neurotically affected. This surely must lead to any family which they may eventually found, also becoming neurotic.

The attacks of bronchial asthma, therefore, might also be regarded as manifestations of a disturbed family life. This naturally entails the consequence that the treatment of these patients should also involve the other members of the family.

Illness is man's reaction to his milieu, in order to create a pseudo-equilibrium. [illegible]

CHOICE AND CHANGE OF PROFESSION

by

D. A. WILLIAMS

The choice of a profession depends essentially on the individual, on his or her educational ability and interest, which is dependant on intelligence, personal drive and steadiness, health, family background and on opportunity Our aim for the asthmatic is to recommend an attainable occupation which will give a reasonable standard of health and happiness and where there is no increased hazard.

Occupational guidance, as has been pointed out by Schwartz (1953) is of special importance to the asthmatic, as occupational asthma often starts at an age in which it is usually an economic disaster to effect a change. He states that a survey of the occupations in which asthma is particularly disabling would be of the utmost value.

Table I shows a list of occupations, or groups of occupations arranged in increasing prevalence of incapacity due to asthma; their sizes in thousands, their certified 'spells of incapacity' in thousands; the 'spells of incapacity' per hundred for each occupational group; and, at the bottom of the list the average for all occupations. By 'spells of incapacity' is meant a period of absence from work for more than four days. The mean duration for asthma was, in fact, fifteen days. The figures relate to males and with certain exceptions cover the working population, the employed and self-employed (plus those who have lapsed from employment). *

The figures have been obtained from the Ministry of Pensions and National Insurance, (Digest of Statistics Analysing Certificates of Incapacity, 1951—1952). The upper eight occupations are all occupations where the amount of incapacity caused by asthma was less than the average and can, therefore, be considered suitable. The ten occupations below the line, all have amounts of incapacity more than the average and are, therefore, unsuitable.

On looking at those listed occupations one may wonder if some occupations owe their positions to their having been avoided and whether others may be over-weighted by asthmatics having selected or drifted into them. It is a possible fallacy, but to what extent this occurs we have no means of estimating, in all probability it is insignificant or at the most, very slight.

* Groups excluded: mariners while at sea, members of the armed forces and non-industrial civil servants.

TABLE I

Occupations listed in order of increasing prevalence of spells of incapacity
Asthma-males (1951) Great Britain

Occupations	Population at risk in thousands	Spells of Incapacity in thousands	Spells of Incapacity per cent
1. Administrators, directors, managers	373	0	—
2. Professional & technical	695	1	.144
3. Commerce, finance & insurance.	1,328	2	.151
4 Agriculture, horticulture & forestry	1,052	2	.190
5. Engineering, metal manufacture.	2,521	5	.198
6. Workers in wood, cane, cork ...	484	1	.207
7. Persons engaged in personal service: hotels, clubs, institutions.	491	1	.204
8. Workers in building & contracting	902	2	.222
9. Fitters, machine erectors	813	2	.246
10 Clerks, typists	793	2	.252
11. Road transport workers	788	2	.254
12. Warehousemen, storekeepers, packers	363	1	.275
13. Electricians, electrical apparatus makers & fitters	358	1	.279
14 Painters & decorators	332	1	.301
15. Railway transport workers .. .	316	1	.316
16. Water, air & other workers in transport & communications .	293	1	.341
17. Workers in unskilled occupations	1,233	5	.406
18. Coal Miners	630	3	.476
All Occupations	14,400	35	.243

Information obtained from the Ministry of Pensions & National Insurance, Digest of Statistics Analysing Certificates of Incapacity, 1951—1952

Calculations checked by E. Lewis-Faning, D. Sc, Ph. D., F.S S, Department of Medical Statistics, Institute of Preventive Medicine, Welsh National School of Medicine.

Another possible error is that some workers may tend to go off sick more readily than others. Some engaged in work entailing only slight physical exertion may continue at work while others engaged in heavy physical work may go off sick with the same degree of illness; financial considerations may also have their effect. These considerations, again, appear to be relatively unimportant, for a person who is able to continue work in a relatively sheltered and economically satisfactory occupation is obviously better off than one who is not.

A third possible fallacy might be if the age-grouping in these occupations varied very considerably, for there is appreciably more incapacity from asthma over the age of fifty years than under fifty years.

Table II shows a comparison of asthma and the infective conditions-bronchitis, nasopharyngitis (the common cold) and influenza. For asthma the positions of the occupations are shown as before; for bronchitis, nasopharyngitis and influenza, the position of each occupation and its percentage 'spells of incapacity' is shown. The percentage for the total population in each illness is shown at the bottom of the respective columns.

Let us take the top eight occupations first There is a large measure of agreement here. Before only three figures can we see plus signs. Workers in building and contracting have a plus thirteen placing in bronchitis, the percentage 'spells of incapacity' being just above the average, 3 55 per cent as against 3.30 per cent. This amount above the average is hardly significant. Workers in engineering have a plus eleven placing in the common cold but here again the amount of incapacity, 1.309 per cent as against 1.306 per cent, is not significant. Workers in wood have a plus ten placing for influenza, with incapacity again only very slightly above the average, 8.0 per cent as against 7.8 per cent. We can see, therefore, that those occupations with less incapacity from asthma than the average, have, with the slight exceptions mentioned, less incapacity from bronchitis, nasopharyngitis and influenza than the average.

In the ten occupations below the line, there is again much general agreement between incapacity from asthma and from these infective conditions. Electricians and painters and decorators are, however, outstanding exceptions. In both these groups of occupations their thirteenth and fourteenth positions in asthma are not in the least in agreement with their relatively high placings in these infective illnesses.

Except, therefore, for these two outstanding exceptions it would indeed appear that the tendency to nasorespiratory infection plays a definite part in the suitability or otherwise of an occupation for an asthmatic.

Comparison of asthma & bronchitis, nasopharyngitis (common cold) influenza, by percentage spells of incapacity per occupational group. Males (1951) Great Britain

Occupations	Asthma	Bronchitis		Nasopharyngitis		Influenza	
	Position	Position	% Spells of incapacity	Position	% Spells of incapacity	Position	% Spells of incapacity
Administrators, directors, managers	— 1	— 1	536	— 1	.268	— 1	1 6
Professional & technical	— 2	— 2	1 29	— 5	.863	— 6	6.8
Commerce, finance, insurance	— 3	— 4	1.58	— 3	.527	— 2	5.1
Agriculture, horticulture, forestry	— 4	— 3	1.42	— 2	.475	— 4	5.5
Engineering, metal manufacture	— 5	—11	3 21	+11	1.309	— 9	7.7
Workers in wood, cane & cork	— 6	— 7	2.69	— 9	1.240	+10	8 0
Workers engaged in personal service (hotels, clubs, institutions)	— 7	— 6	2.65	— 4	.611	— 2	5.1
Building & contracting	— 8	+13	3 55	— 7	1.109	— 7	7.1
Fitters, machine erectors	+ 9	—10	3 20	+15	1.599	+15	8.7
Clerks, typists	+10	— 9	2.90	+13	1.39	+14	8.4
Road transport	+11	12	3.30	—10	1.269	+13	8.3
Warehousemen, storekeepers	+12	+14	3.86	+17	1.653	+10	8.0
Electricians	+13	— 6	2 23	— 8	1.117	— 8	7.5
Painters & decorators	+14	— 8	2.71	— 6	904	— 5	6 0
Railway transport	+15	+15	4.11	+14	1 582	+17	10.1
Water, air & other transport	+16	+16	5 12	+12	1.365	+12	8.2
Unskilled	+17	+17	5 92	+16	1.622	+16	8 8
Coal Miners	+18	+18	8.1	+18	5.556	+18	18 0
Average spells of incapacity			3 30		1 306		7.8

— Indicates that the incapacity is less than the average for all occupations + Indicates that the incapacity is greater than the average for all occupations

Information based on figures obtained from the Ministry of Pensions & National Insurance Digest of Statistics Analysing Certificates of Incapacity, 1951—1952. Calculations checked by Dr E. Lewis-Faning, D Sc, Ph D, F S S, Department of Medical Statistics, Institute of Preventive Medicine, Welsh National School of Medicine, Cardiff

Table III compares the position in asthma with the positions and 'spells of incapacity' expressed as a percentage of each occupation in nervous debility and in psychoneuroses and psychoses, that is, with illnesses due to nervous upsets. (I am sorry that the figures for psychoneuroses and psychoses were not split up). Let us take the top eight occupations first. All these occupations have position in these illnesses which are better than the average.

In the lower ten occupations, again except for electricians and painters and decorators, there is general agreement between illnesses due to stress and asthma.

Table IV lists all the illnesses we have been discussing in order of increasing incapacity.

The comparison of these figures is not without interest. Administrators, directors and managers have the least incapacity in asthma, in the infective respiratory groups and in the psychological groups.

The terms administrators and directors need no explanation, but the term manager needs a little amplification. In the main managers include all those in executive positions drawn from all occupations including industrial occupations such as mining, chemical, engineering and building, etc., i e. when they cease to work in these occupations as such and take up office work. In this group are the financially and socially successful. It would appear that financial success must play a large part in the prognosis of asthma. Responsibility, success, good food, good homes with low physical demands, have no ill effect on asthma, in fact these appear to be the most desirable attainments for the asthmatic.

Professional and technical occupations are also eminently satisfactory for asthmatics. These occupations include the recognized professions, the Church, Law, Medicine, as well as medical auxiliaries, teachers, professional engineers, surveyors, architects, statisticians and mathematicians, authors, editors, journalists and officials of political, industrial and trade associations. As with the previous group, these occupations are in the main in the upper social classes.

Commerce, finance and insurance, again a satisfactory group of occupations on all counts.

Commerce includes commercial travellers, proprietors of commercial concerns and their salesmen and their shop- and other assistants, i.e. those working in the wholesale and retail businesses, e.g. grocery, green grocery, meat, fish, poultry, confectionery and miscellaneous stores. Finance includes company directors, bankers, stock brokers, auctioneers and estate agents. Insurance includes insurance managers, underwriters, brokers, agents and canvassers.

Agriculture, horticulture and forestry is among the most suitable occupations for asthma and all the other diseases listed. This group

TABLE III

Comparison of asthma & nervous debility, psychoneuroses & psychoses by spells of incapacity

Asthma-males (1951) *Great Britain*

Occupations	Asthma	Nervous Debility		Psychoneuroses & Psychoses	
	Position	Position	% Spells of incapacity	Position	% Spells of incapacity
Administrators, directors, managers	1	— 1	—	— 1	.268
Professional & technical	2	— 8	.288	— 5	.432
Commerce, finance, insurance	3	— 5	226	— 3	.377
Agriculture, horticulture, forestry	4	— 2	.095	— 2	.285
Engineering, metal manufacture	5	—13	.357	— 7	.555
Workers in wood, cane & cork	6	— 4	.207	— 4	.413
Workers in personal service (hotels, clubs, institutions)	7	— 3	204	—10	.611
Building & contracting	8	—11	.332	— 6	.554
Fitters, machine erectors	9	+14	.369	+13	738
Clerks, typists	10	+15	.378	+15	.883
Road transport	11	+16	.381	—12	635
Warehousemen, storekeepers	12	— 6	275	+14	.826
Electricians	13	— 7	279	— 8	.559
Painters & decorators	14	— 9	.301	— 9	.602
Railway transport	15	—10	.316	—11	633
Water, air & other transport	16	—12	.341	+17	1.024
Unskilled workers	17	+17	.649	+16	973
Coal Miners	18	+18	1.11	+18	1 43
Average spells of incapacity			.361		.660

— Indicates that the incapacity is less than the average for all occupations.
+ Indicates that the incapacity is greater than the average for all occupations

Information based on figures obtained from the Ministry of Pensions & National Insurance: Digest of Statistics Analysing Certificates of Incapacity, 1951—1952 Calculations checked by E Lewis-Faning, D. Sc, Ph D, F S S, Department of Medical Statistics, Institute of Preventive Medicine, Welsh National School of Medicine, Cardiff.

TABLE IV

Asthma, bronchitis, 'colds', influenza, nervous debility, psychoneuroses & psychoses

Asthma-males (1951) *Great Britain Table listing positions of occupations*

Occupations	Asthma	Bronchitis	'Colds'	Influenza	Nervous Debility	Psychoneu-roses & psychoses
Administrators, directors, managers	— 1	— 1	— 1	— 1	— 1	— 1
Professional & technical	— 2	— 2	— 5	— 6	— 8	— 5
Commerce, finance, insurance	— 3	— 4	— 3	— 2	— 5	— 3
Agriculture, horticulture, forestry	— 4	— 3	— 2	— 4	— 2	— 2
Engineering, metal manufacture	— 5	—11	+11	— 9	—13	— 7
Workers in wood, cane & cork	— 6	— 7	— 9	+10	— 4	— 4
Workers in personal services (hotels, clubs, institutions)	— 7	— 6	— 4	— 2	— 3	—10
Building & contracting	— 8	+13	— 7	— 7	—11	— 6
Fitters, machine erectors	+ 9	—10	—15	+15	+14	+13
Clerks, typists	+10	— 9	+13	+14	+15	+15
Road transport	+11	12	—10	+13	+16	—12
Warehousemen, storekeepers	+12	+14	+17	+10	— 6	+14
Electricians	+13	— 6	— 8	— 8	— 7	— 8
Painters & decorators	+14	— 8	— 6	— 5	— 9	— 9
Railway transport	+15	+15	+14	+17	—10	—11
Water, air & other transport	+16	+16	+12	+12	—12	+17
Unskilled	+17	+17	+16	+16	+17	+16
Coal Miners	+18	+18	+18	+18	+18	+18

— Indicates that the incapacity is less than the average for all occupations.

+ Indicates that the incapacity is greater than the average for all occupations.

Information based on figures obtained from the Ministry of Pensions & National Insurance. Digest of Statistics Analysing Certificates of Incapacity, 1951—1952. Calculations checked by E. Lewis-Faning, D. Sc., Ph. D., F.S.S., Department of Medical Statistics, Institute of Preventive Medicine, Welsh National School of Medicine, Cardiff

includes farmers, gardeners, forestry and horticultural workers and those with ancillary occupations to agriculture. Their increased exposure to extrinsic allergens such as pollen and mould spores, and in some cases animal danders, does not appear to affect them appreciably as a group as regards incapacity. One wonders if asthmatics do tend to avoid these occupations These figures show no reason for avoiding agriculture, but on the contrary suggest that asthmatics might be encouraged to take up agriculture.

The next group, engineering and workers in metal comprises a very wide and large group, varying from furnacemen, foundry workers, smiths, metal workers of various types, to scientific instrument makers and workers in precious metals. Although the 'spells of incapacity' for asthma in this group is satisfactory, this group has a higher tendency to infections and a slightly higher tendency to nervous upsets than the position occupied in asthma would warrant. As a group this has a satisfactory placing in asthma, but one might well consider what branch or sub-group the asthmatic is advised to take, so that the tendency to infection would be less than the average for the group, nor should the psychological suitability, the economic return of the work, and the chances of promotion to the administrative or managerial positions be ignored

Workers in wood, cane and cork comprise a comparatively small group In general it is a fairly satisfactory group and its position in this list is, perhaps, not surprising.

Personal service, i.e. workers in homes (domestic of all types), in hotels, restaurants, clubs and institutions, and includes hair dressers, photographers and laundry workers—all who give a personal service Again a fairly satisfactory group of occupations for asthmatics, having a higher position than perhaps we, as allergists, might have suspected.

Building and contracting needs little explanation. As the prevalence of bronchitis in this group is higher than normal, asthmatics in this group should take extra care to avoid respiratory infections.

Fitters, machine erectors, includes tool makers and fitters, fitter-assemblers, maintenance engineers, motor mechanics and other machine erectors and fitters. You will notice the marked tendency to influenza and the relatively high rate of nervous upsets.

Clerks and typists. This, of course, refers to men only and it surprised me that it was so low in the list. It includes costing, estimating and accountancy clerks, secretaries, but not company secretaries and office machine operators Essentially they work in an office, the same as administrators, managers and directors, except that they rarely have an office to themselves and their economic position is obviously much lower. Their tendency to upper respiratory infection is comparatively

high, as is their tendency to nervous manifestations. Their comparatively low position in our asthma list is probably associated more with their economic state than with their actual working conditions. One might have wondered if some asthmatics might not have drifted into these occupations, but the evidence would appear against it.

Road transport, eleventh, causes less debility from asthma than does railway transport or water and air transport, presumably due to the fact that they are in their lorries, have less physical exertion and less direct exposure to the elements.

INFORMATION OBTAINED FROM MINISTRY OF PENSIONS & NATIONAL INSURANCE DIGEST OF STATISTICS ANALYSING CERTIFICATES OF INCAPACITY 1951-1952

PERCENTAGE OF SPELLS OF INCAPACITY CAUSED BY ASTHMA



Warehousemen, storekeepers, packers of furniture, china and glass and bottlers. Here again, is an unsatisfactory group of occupations and their position on the list of asthma fits in with the other illnesses. There is a very high incidence of the common cold in this group. Here again, one wonders whether people who have become, or originally were, somewhat incapacitated have been attracted to this type of work, but the correlation of incapacity between asthma, infection and stress in the group is against this.

Electricians and painters and decorators. It is of special interest

that in the infective and stress illnesses they have a consistently and considerably higher placing than in asthma. Many painters and decorators and some electricians, are undoubtedly excessively exposed to that very potent allergen house dust. Fumes from paints and non-specific dusts in both occupations may also play a part. Economically they are about average. The other alternative is that many asthmatics have chosen these occupations, but this appears unlikely. Whatever the reason, we must consider these occupations unsuitable for asthmatics.

The last two groups are obviously the worst, not only for asthma but for the other illnesses listed. The figures here are quite consistent. Economically the wages in coal mining are relatively good and their position as the worst occupation is probably entirely due to their work.

I would, however, draw your attention especially to the lowly position of the unskilled workers. I have, for many years, urged asthmatic children to work hard at school, to develop mental capabilities to compensate for their physical disabilities. In asthmatics at work, I urge them to be conscientious and thorough, to develop steadiness and personal drive so that they do not change their occupations frequently and so end up in this group of unskilled workers.

Finally, the map shows that in Britain, the place of occupation for males also significantly affects incapacity from asthma. It shows that there is less incapacity from asthma in the South East districts of Britain (the warmer and drier parts) than in the western and northern districts (the wetter and colder parts). Therefore, in choice or change of occupation, the locality should also be considered. This latter consideration may be especially considered in the middle-aged asthmatic, where a change of locality may be more easily brought about than a change of occupation or profession.

In summary, I would suggest that in the choice or change of profession we should consider: 1. the resulting economic position; 2. the liability to naso-respiratory infection; 3. the liability to stress, and last, but not unimportant; 4. the liability to extrinsic allergens, as well as the locality.

It is with pleasure that I acknowledge my indebtedness to Dr. Lewis-Faning, D Sc , Ph.D , Department of Medical Statistics, Institute of Preventive Medicine, Welsh National School of Medicine, Cardiff, for his help and advice with the figures presented.

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SCHWARTZ, M (1952) *Acta allergologica, V* Supplement II.

flour allergy leading step by step from a rhinitis over bronchial asthma to an emphysema. However, the workers in the spinning mills will usually not live to this late stage of the disease, since they will become transferred after their first asthmatic episodes (although even then too late) into rooms clear of sericin: dyeries, packing-rooms etc.

Every worker ought to be examined as much as every miller and baker, every 3 or 6 months for the symptoms of sensitization (skin reactions or other manifestations). If positive findings exist, the person affected should be withdrawn from this type of work and, if feasible, be given another occupation.

[illegible]

demic' asthma occurs in the vicinity of factories in which castor-beans are processed while their dust is expelled into the open air. However, the disease will not become evident among persons who recently moved in the surroundings of the factory but only among those that lived there for a certain length of time. This span represents the sensitization period Sensitization will not occur unless the dwelling lies within the reach of the gaseous by-products with their allergen-bearing dust particles Thus the 'epidemic' originates by means of temporary exposure to the allergen,—comparable to the spreading of an epidemic of typhoid by the dissemination of the typhoid bacillus through contaminated water, milk or the like. I myself[1] have examined such cases, and more asthmatic epidemics owing to the dust of castor-beans have been described in U.S.A. bei Figley and Elrod,[2] Zerbst[3] and a new by A. U. Cintra und E. Mendes.[4] Important are the corresponding experiments by Ratner and Gruehl [5]

4) The same principle of pathogenesis is also realised in 'Printer's asthma' (Hoschek,[6] Fowler[7]), although the allergen is a different one. it is represented in the gum arabic *resin*, used as powder in the process of wet spraying. The symptoms of this disease gradually develop in the same manner as in the 1st and 2nd example.

5) Mention is also made of the asthma arising in factories producing *mother of pearl-buttons*. Here the principle works according to the allergy to oyster-shells described by W. Gronemeyer[8]; detailed description hereof is given on the First International Congress for Allergy, Zurich (see fig 2 and 3).

6) There exist some more observations on this subject which will not be considered here as I am presenting only own contributions or some few clear cut communi-

[1] *Hefte zur Unfallheilkunde, 44* (1952), S. 221
[2] *J A.M A. 90* (1928), 79
[3] *Industr Med 13* (1944), 552.
[4] *J Allergy, 25* (1954), 253.
[5] *Am J. Hyg 10* (1929), 236.
[6] *Polygraph, 1953*, S 611 (Heft 20)
[7] a) *Lancet, 16* (1952), 755 b) Intern. Arch. Allergy etc. 6 (1955), 120
[8] *Ist. Intern. Cgr Allergy*, 1951, Proceedings p. 285.

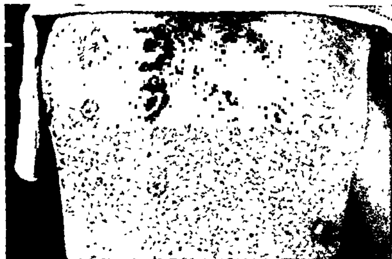
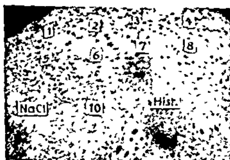


Fig 1



	Antigen in 0 9% NaCl		Antigen in autoserum 1 40	
	1 10	1 100	1 10	1 100
Fleshy part of oyster	○	○	○	○
Oyster-shell	○	○	(+ + +)	○
	○ 0 9% NaCl		○ Autoserum 1 10	(+ + +) Histamine 1 10 000

Fig 2



Prausnitz-Kustner reaction					
Injection after 48 hours					
	with antigen (oyster-shell) in 0 9% NaCl		in neutral serum		without antigen
	1 10	1 100	1 10	1 100	neutral serum
Pre treated with inactive serum no antibodies	○—	○—	○—	○—	○—
Serum of patient antibodies +	○—	○—	(+ + +)—	○—	○—
Not pre-treated 1st test	○	○	○	○	○
2nd test	0 9% NaCl ○			(+ + +) Histamine 1 10 000	

Fig 3

cations to the problem as given in the scientific works of Royle[1], Wyers[2] and others: asthma from dust derived from cotton-seed, sheep's wool, coco-nut fibre etc.

All these observations stress the significance of the *invasion by some allergen* for the pathogenesis of bronchial asthma. Whatever gets registered as bronchial asthma either in our clinics or in general practice is based on the same principles. Unfortunately there are so many cases of allergy with a long history the clinical symptoms of which became overflowing only now or went unnoticed for years although fragments of the process existed long before. Every year the number of allergic persons augments among which the analysis of some antigen is successfully performed demonstrating a specific cause of the disease. Yet, these analyses [illegible] fragments and the complete syndrom of [illegible]

[illegible]

which formerly were said to be the [illegible] of a hyperergic inflammation due to [illegible] virus. Although the conception [illegible] its correct use is not too frequently encountered. Thus the old [illegible] esteem This fact also often [illegible] However there exists [illegible] asion by a common [illegible] he formation of an [illegible] must be stressed that [illegible] he pathogenesis of [illegible] the focus of [illegible] ase ranging [illegible] strating the [illegible] elaborated, it is not [illegible] allergen. However the more skilful and exact the [illegible] findings observed, the richer the findings will [illegible] *istics* can barely be that con[illegible] iternal and external additional [illegible] occupational asthmatics, these [illegible] success[illegible] formed [illegible] irritated [illegible] ttained. [illegible] condary [illegible] chronic [illegible] is, fixed lesions of the mucous membrane [illegible] bronchitis, derangements of innervation (pathological [illegible] conditioned reflexes), harder organic lesions such as emphysema and bronchiectasis are irreparable. Tissues of low functional value as scar tissue have then replaced the normal tissue with its regular function.

For these *heavily* damaged asthmatics symptomatic therapy granted by drugs,

[1] *1st Intern Cgr. Allergy*, 1951, Proceedings p 76

[2] *Intern. Arch. Allergy*, 6 (1955), 119

gymnastics, psychotherapy, changing of environment and climat means a certain but not entirely satisfactory relief

If the described connections would become generally acknowledged the importance of the patient's history recognized and the gradual development of the disease comprehended, then the first symptoms could be traced back to a (possible) allergy. An analysis of the allergens could be achieved and on the basis of protection from the allergen further damage—particularly the incurable final stages of the disease—might be readily prevented.

INHALATION RISKS OF FUNGAL SPORES TO BUILDERS AND DECORATORS

by

K. MAUNSELL

Since a high percentage of patients suffering from bronchial asthma with house dust and fungus allergies was found among builders and decorators, quantitative estimation of the concentration of airborne spores was carried out in 2 London houses under structural repair and compared with 6 normal dwellings (slit sampler) Sampling was carried out in a room adjacent to the one in which the builders were working. The rooms had no direct communication but led to a common hall. A tenfold increase was noted in the total spore count inside dwellings when building was in progress The increase was mainly due to Penicillium. It must be assumed that the concentration of airborne spores in the room in which the men were actually at work was considerably higher and that prolonged exposure to such air may well lead to asthma in allergic builders and decorators.

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MAUNSELL, K (1954) *Internat. Arch of Allergy and Appld. Immun. 5*, 373

B. STOKVIS

The experiences in our Leyden Psychosomatic Center proved that, in several cases, difficulties and frustrations in the profession are of more importance than those *in sexualibus*, which are often considered as the most important psychic determinants in patients with asthma. We always try to combine our psychotherapeutic measures with the case-work of our (female) social worker. The latter visits the employers and tries to improve the social situation and environmental factors in close co-operation with the psychotherapist.

R. S BRUCE PEARSON

In considering the figures that Dr. Williams has shown us, it is important not to over-simplify their significance. Although certain occupations may predispose to asthma, it is also probable that certain occupations are more suitable for asthma-

ties than others and these will, therefore, have a high incidence of asthmatics among them. Many young asthmatics, for example, take up clerical work, because they feel it will be within their capability. Because there is a relatively high incidence of asthma among clerks, it does not, therefore, necessarily mean that this occupation predisposes to the development of asthma

D. A. WILLIAMS

The natural history of asthma is to start in childhood, to tend to disappear in the teens and in young adult life and to come back again in later life. When we advise individual asthmatics in their choice of occupation we must obviously not advise an occupation where there is a big risk of allergic sensitization, such as bakers, printers, etc , and I would agree with this. It is, however, important that we should take a very broad view of the choice of occupation for an asthmatic for in this way we can hope to prevent the return of asthma in later life in many cases, asthma which so often leads to much incapacity.

The miners in England and Wales are frequently x-rayed and the incapacity listed as due to asthma could not be due to pneumoconiosis.

CHILDREN'S HOMES FOR ASTHMATICS*

by

SVEN KRAEPELIEN

Nowadays asthmatic children are a large part of the patients in our children's hospitals and in the offices of pediatricians. As far as we can judge, the number of asthmatic children has increased considerably during the last few decades, even though we cannot get any exact figures. In an investigation of the incidence of asthma in the Swedish schools, I have calculated that the number of asthmatic children in our little country is about 10 000. In the elementary schools of Stockholm the incidence was about 1.4 per cent. When the asthmatic children of pre-school age are also taken into account—a very large group whose exact number cannot be definitely established—the serious pediatric and social problem of asthma becomes even more obvious. Similar figures for frequency are to be found in Norway and in Holland.

For technical and, many times, for psychological reasons asthmatic children are usually investigated at the hospital and the treatment is generally started there. A frequent and regular control is always necessary, which is upsetting for the child as well as for its parents. Unfortunately it is often necessary to discharge children from the hospital at a time when, for various reasons, it is not convenient for them to return to their homes. A satisfactory adjustment of the home environment from an allergic point of view is not always possible, for instance, because of the father's profession or unfavourable home conditions. Small apartments with difficulties concerning good dust hygiene increase the risk of infections. During the treatment period there should always be the possibility of placing this group of children for various lengths of time away from the family in a suitable home, like a convalescent home. It is true that asthmatic children can stay in ordinary convalescent homes together with other children, but the character of their illness is always a hindrance to their being admitted to the home. Often the personnel is afraid to handle the acute attacks of the asthmatic children. Also, the length of time the children are allowed to stay at these ordinary convalescent homes is limited by the lack of places there. At least this is the case in Sweden and I suppose this is also true in many other countries. For asthmatic children, a two or three weeks' stay away from their home environment is not sufficient; often they

* From the Pediatric Clinic of Karolinska Sjukhuset, Stockholm. (Head Professor A. Wallgren).

often become quite free from symptoms as soon as they come to the hospital without any therapeutic measures at all. A hygienic environment from an allergic as well as a psychological point of view is the probable explanation. Since 1936 a boarding school for about 20 asthmatic children has existed in Stockholm. The home is situated in Stockholm itself and is only a few metres above the sea. First, the equipment of the home has aimed at a rational dust hygiene. The children live there during the school terms and usually get leave of absence every weekend. In the summer, when most asthmatic children have their best period,—except those sensitive to pollen—the children usually stay at home or at public summer homes together with other children. The shortest time of attendance has been one term and the longest, 14 terms. During the first days after their arrival at the home most of the children have become free from their asthma attacks. All have been able to complete their school attendance, interrupted, of course, by intermittent illnesses, but less often by asthma attacks. During their stay at the asthma home all the children have received aspecific desensitizations with colloid sulfur, sometimes combined with bacterial vaccines-therapy. In a follow-up study with an average observation time of 3–4 years it is seen that about 90 per cent of the children from the asthma home have become free from attacks that had badly influenced their condition or occupation. The good results from the asthma home in Stockholm are quite as good as those from mountain asthma homes, even though the published results cannot be compared in all respects.

As not all countries have the desired topography for such homes in the mountains, I want to stress as my personal opinion that it is not necessary for such homes to be at higher altitudes far away from home environments and, above all, quite inconvenient.

With the high incidence of asthma in children today in most countries, it is desirable that a sufficient number of suitable institutions is established so that more children who need such care may have this advantage. In Sweden the interest in this matter has had good results during the last few years. In the spring of 1955 the Swedish Red Cross started another school home for asthmatic children and in several Swedish provinces they are preparing similar institutions.

What are the requirements for an asthma home? An asthma home should be centrally located in the neighbourhood of a big town or in the center of a province. As climatologic factors have hardly any decisive importance for the asthmatic children, there is no reason to place the home in high altitudes, which often means transportation for longer distances and thus, more inconveniences. A good reason for a central position of an asthma home is first the need for close contact with pediatric hospitals. As the child with acute attacks should have the

possibility of immediate hospitalization, the relative proximity to a hospital must be the decisive factor in its location. The parents must have the security of knowing that their child will be able to get help and adequate attendance when having an asthma attack. Another important reason for the central location of an asthma home in a town or a province is that the parents will be able to visit the child rather frequently. This is specially important for the preschool child, as a long separation from home and parents may have a detrimental effect on the child's health in the long run, an extremely important circumstance, only recently given the proper consideration. The parents thus have frequent assurances of the child's welfare and may observe with their own eyes in what environment he is living.

In every asthma home it should be possible for the children of school age to attend classes. Classes can of course be held in the home itself, but as a rule such arrangements make the costs higher. It is less expensive and often quite sufficient if the children can have their education at a nearby school. In a large city where there are more extensive educational facilities and better possibilities for collaboration with school authorities, this problem of co-operation between school and home can be solved practically so that more or less irregular pupils may continue their studies.

The duration of the asthmatic child's stay at the home should not be fixed in advance but should be determined by the individuals need. The time of attendance should not be shorter than 3 months, that being the shortest period with any therapeutic importance.

A further requirement for an asthma home is that there must be a specialized nursing personnel Even at the home the children should be able to get the help they need for their attacks To avoid any insecurity in their minds the parents must be convinced that there is a competent personnel at hand. If there is not a competent staff one can very well understand the parents' hesitancy in sending their children to the home. The parents know more than anybody else that their child needs special care The home should be under the guidance of a physician, preferably a pediatrician

In spite of the inconveniences that separation of children and parents may bring about, the many good results we observe when taking asthmatic children from their home surroundings for varying lengths of time, suggest that we always should have available the facilities to do so whenever indicated. Even if the stay in special asthma homes —whether mountain or city—does not bring about more constant results, it often gives the children an interval in which they feel better and more like other children Their physical and psychological condition

often improves and may facilitate the continued therapy in their own home environment.

SUMMARY

With respect to the high incidence of asthma in children the author discusses the need of special homes for asthmatic children, and the importance of a change of environment for some of these children as a necessary part of the therapy. The placing of asthma homes at high altitudes in the country as opposed to the more convenient city locations is discussed. The author himself prefers the last mentioned alternative and presents his reasons.

THE INSTITUTIONAL REHABILITATION OF THE INTRACTABLE ASTHMATIC CHILD

by

H. S TUFT

Fifteen years ago, a definitive program for the institutional rehabilitation of the intractable asthmatic child was started at the Jewish National Home for Asthmatic Children, Denver, Colorado. This program was conceived by Dr. M. Murray Peshkin,[1] who in 1930, expressed the need for such an institution. In the course of this operation, certain concepts of the development of intractable asthma have been recognized. There has been also an attempt to define the reasons for the obvious results inherent in this procedure. This paper will attempt to cover both phases so as to provide a basis for further discussion in this field.

In the early days of this program, it became apparent that separation from the home environment was effective in controlling asthma in approximately forty-two per cent of the children admitted to the institution These children would have no further asthma during their stay which usually was a two-year period. A second group, comprising forty per cent of those admitted, showed progressive lessening of severity and frequency of symptoms in the first year of residence and complete loss of symptoms in the second year. The remaining 18 per cent of the children were either not helped at all, or learned only to tolerate the symptoms already present.

The immediate cessation of symptoms upon arrival at the Home in the group so affected gave rise to speculation concerning the reason for this result. A theory of the development of intractable asthma was developed which included the following factors: heredity, allergy, infection and finally, the emotional overload. It would be redundant to cover the first three factors, but the fourth factor needs a great deal of clarification

By the term 'emotional overload' is meant the additional burden carried by an asthmatic child in a disturbed, unhappy or tense home environment It has been postulated that such a burden may be the one single factor which converts an ordinary asthmatic child into one who will not respond to conventional anti-allergic therapy. It has been further postulated that the emotional environment may actually cause a break-down of the immune mechanism. There is the probability that ten per cent of asthmatic children fall into the category of intractable asthma. One should not, however, conclude from the foregoing that

the lessons learned in the intractable asthmatic necessarily need apply to all asthmatic children.

It is our feeling that the type of emotional overload which most of these children manifest, is described quite completely by Abramson's concept of the 'Cronus complex'.[2] Although the theory of maternal *rejection as proposed by Miller an Baruch*[3] *has been widely circulated*, we cannot see the application in our patients at the Home. We believe that maternal rejection is part of our twentieth century culture and is common in all child-parent relationships We feel that there is no greater incidence of this symptomatology in the asthmatic child, and further that this symptom is not responsible for the production of the intractable state.

Certain technical matters should be discussed at this point in order to clarify the matters of admission procedure and the discussion of the application of treatment technics The age of children to be admitted is restricted to those five years of age, up to and including 16 years. Younger children have not been admitted because of the tremendous cost of the custodial problems involved. Older patients cannot be admitted because the physical plant does not allow for adequate supervision of the older teen-ager

The sole medical criterion for admission is the diagnosis of intractable asthma. Intractable asthma is defined as severe, perennial asthma, requiring frequent hospitalization which continues despite adequate, sustained therapy including complete allergic workup.

To make maximum use of treatment in the institution, a sick child must be ready to separate from the family. The child must have the capacity to live in a group situation. The IQ must be in the normal range, for those with subnormal IQ ratings cannot make maximum use of psychiatric casework The family must be able to allow separation and must be willing to continue in a casework relationship while the child is under care This study is made by the casework agency (family welfare, child welfare or child guidance) in the hometown of the patient.

The Home is located on a 17½ acre tract in the heart of Denver. Children reside in cottage-type buildings with each child having an individual room or a cubicle. Each cottage is supervised by a house father or a house mother, usually in the number of one house parent to ten children. The children attend public schools in the vicinity. The grade school is located approximately four blocks from the Home, the Junior High School is across the street from the Home and the High School is within walking distance of the Home. The staff also includes a full-time athletic director and part-time recreation personnel.

Four features of treatment and rehabilitation are recognized. The simple matter of separation from the home environment is perhaps the

most important in the eventual rehabilitation. It should be stressed that this in all probability represents a tremendous total environmental change which includes both freedom from contact with allergens as well as removal from emotional tension of the home. The word 'parentectomy' has been coined by Doctor Peshkin to describe one feature of the separation. This alone cannot account for the immediate result, but may be responsible for some of the long term results.

The matter of climatic change comes in for a great deal of discussion but there are many features of the weather in Denver that mimic to some extent those in home communities. Generally speaking, the Denver climate is drier, there being many more days with humidity being less than 20 per cent. However, there are wide temperature swings from day to night and periods of precipitation and gale-like winds which also are present in other areas of the country. The altitude of Denver is 5280 feet above sea level, but it must be stated that this has never presented any problem with regard to respiratory function.

The next facet which is deemed of importance is the matter of group living. *It is now a well-recognized fact that children afflicted with* chronic disease do much better in an institution dedicated solely to that disease rather than in a general institution. There is a great deal to be said for the ability to look at one's neighbour with similar afflictions without shame or reproach.

Many children have been hospitalized frequently or have spent many hours in bed. They have forgotten what it is like to play with other children. Institutional living helps in this field as well as in the field of new adult experience and restoration of confidence House parents assigned to each group are educated in the physical and emotional aspects of asthma so as to view the child in a different perspective than his own parent. The child reacts to this attitude with a calmer, less harrassed feeling which aids his eventual rehabilitation. Athletics, arts and crafts, and music training are other facets of the group living approach

It would not be in the scope of this paper to discuss allergy therapy in general. Suffice it to say that the recognized technics of testing and treatment are utilized in the institution much in the same way as in the child's own area. We have seen many instances of pollen therapy becoming effective during their residence at this institution whereas it was apparently ineffective previously.

The success of the role of the psychiatric therapy in eventual re- [illegible]
s
n
institutional setting. The degree of psychiatric therapy depends upon

the problems presented. It is our feeling that the highly trained social worker from an approved school of social work and having at least a master's degree in the field is capable of handling most of the problems connected with adjustment to the institution, and to the living situation. However, therapy which need go beyond this more or less superficial approach should be done by analytically trained psychiatrists. Psychiatrists must, however, have special adaptation for the work of children and a very good orientation in the asthmatic individual's problems in order to become completely effective in such a setting.

The members of the social service staff work with those in other departments to help the child make maximum use of placement in the Home. This is accomplished primarily in three ways:

1) The social service worker reviews the child's history and contributes his observations to the people who are working more closely with the child. In this way each adult having contact with the child gains a more complete understanding of him. This interchange of knowledge and impressions aids greatly in planning the future treatment of the child.

2) The social service worker keeps the parents informed of the child's general adjustment through reports to the social agency. These reports enable the agency to help alleviate the parents' concern about the child, and to help the parents in reaching a better understanding of their own problems.

3) The social service worker holds regular interviews with the child. These interviews compose the greatest, and perhaps most important, part of treatment. The permissive setting of the office enables the child to express himself through talk and play. The relief of emotional tension this therapy provides makes the child more responsive to other treatment; enables him to adjust more readily to the institution; and prepares him for his eventual return to his family.

Space does not allow a more complete evaluation of the total result. However, in general, it might be said that 85 per cent of the children in the program have maintained their gains for up to 12 years. Followup studies should be available to the profession within the next two years in the form of a monograph by Doctor Peshkin which is presently being written.

The indication realized from this 15 year experience is that more facilities must be available for children falling into this category. Pending a greater knowledge as to the reason for the effect of separation, rehabilitation of the intractable asthmatic child must be expanded to include those patients restricted from this approach by reason of financial responsibility of the parents. One may foresee the need for institutions of this kind in each country of the world as well as in connection with the large cities of the United States.

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DISCUSSION

IS IT USEFUL TO MAINTAIN NURSING-HOMES FOR CHILDREN?

by

N. J. M. AARTS

A change of appreciation of the Nursing-home for Children may be seen nowadays. In the beginning mostly only badly nourished children were sent to a home for a while—normally 6 weeks—to rise their weight by good food and by dividing the day [illegible]
homes f [illegible]

To-da, [illegible]
comes more and more into the list of indications is nervosity It means that a child is not capable of living its normal everyday life as it should: it is badly tempered, does not eat, does not grow, does not behave itself in the normal way, does not sleep or awakes several times during the night with fear, is lightly influenced by misfortune etc Mostly the cause of this abnormality lies in the family.

Is there any reason to treat these children in a home?

The cause—the incongruities of the family—cannot be cured by removing the child and forstering it during a period of several weeks in a nursing-home. Still, I believe, we can do much good by giving these children a time of psychical rest outside the family, even when knowing that a return to there will be necessary.

Until now I spoke about nervosity, but the same is true for asthma, because next to other factors, a mighty psychical component is there Therefore, apart from the fact that medical care is necessary in the 'normal' nursing-home and special medical care in an asthma-center, the most important thing we have to do is to give these children a mental-training, without letting them know it is a mental-training We can give them a better adaptation to reality, we can teach them how to behave themselves with other people, in the first place of course with other children, but also in their contact with grown-up people. These 6 weeks—often twice as much—are as important to the child as a holiday of some weeks is to a working man. And beyond this holiday we can give them so much!

For that reason in the nursing-home there must not be a system as in a military camp The child is, mentally, unable to accept all it does not understand We must try—according to its capacity to understand—to show and teach the child why it has to behave the way we tell them and not in any other way! We must [illegible]

... the children a good time for 6 or 12 weeks; but after

to decide where and how to stand against the troubles in its family.

Therefore we must think—more than we have done before—about the family. While the child is in the home and better already before, we must ask the help of the social-worker! At first this person must make a report of the family, social, structural etc This report must be sent, also, to the doctor of the nursing-home—in that case he can talk it over with the directing nurse and as a result of this the report might be of some help in the treatment of the child Next the social-worker must try to change the family-situation in talking with the parents, separately and together Often it will be no case for the social-worker, but more for the psychiatrist. Thus there must be co-operation between the family-doctor and the

of keeping contact with the nursing-home for two reasons:

1) the nursing-home can give—also afterwards— some good advice

The nursing-home itself must be, as much as possible, a normal home. It must not be too splendid, with too much of a home in a nursery-tale It must not be too big a change for the children from the familyhouse into the nursing-home, and back again. Give them the same things to play with, that they know from home. Do not let them sleep in a room with too many beds, do not make a dormitory—personally I like bedrooms for about 6 children And, as it is a home, let them have the feeling that, when in trouble, there is always someone to help them—like mother at home Do not let them play all day long what the nurse in charge likes to do, but give them also some time to do as they like.

In this way I believe, all our nursing-homes have reason to exist, and we cannot miss them!

As a result, the youth of to-day will be the psychical stronger generation of to-morrow.

J. DUCHAINE

From a limited experience with an asthmatic children's home, established at the Belgian Coast, the author draws the following tentative conclusions.

It is desirable that the Home should be constructed in view of its special purpose. Attention should be directed to the facilities necessary for play in allergen-free surroundings.

Problems arising from adequate schooling should be considered as the children have to spend at least 6 months in the home before they can be sent back. During

their stay, adequate desensitizing treatment should be given and the child should only return in his family if control of environments in his own house has been fulfilled.

Diagnostic elimination diets can be used in the home although they necessitate full co-operation from the staff and the hotel management. This last point is sometimes difficult to attain.

THERAPEUTIC VALUE OF ASTHMA-HOMES

by

J. E. C. SCHOOK

A certain percentage of the children with bronchial asthma is at home resistent against every form of treatment. All therapeutic measures, we take, fail and we can't succeed at home in trying to get a reasonable situation.

These are the children who in the first place are considered for an admission to an asthma-home and with these children is such an admission, which means a long separation of the child from his family, mostly justified.

Why is it possible to treat these children better in an asthma-centre than in their own homes?

Of course there are many advantages, which are very clear. In the houses specially fitted for these children we can make the conditions of life as favourable as possible This concerns as well the allergic factors as the psychological sides of asthma.

I shall not go into this subject But there is still one thing, I think is very important which I will mention in this connection, and which shows in my opinion the value of the asthma-centre very obviously and that is the possibility for an exact observation of the patient and of his attacks of asthma. By this observation it often becomes possible to find out which factors are important for his type of asthma and how we have to treat them

You all know how difficult it often is to get a clear history from the parents of the asthmatic child and to form a just notion of the different factors, which take part in the influences on the attacks of the child.

When we have the child under our constant observation we can note very exactly his attacks and all influences which may be important. In this way it is often possible to get a better view on the patient and his sensibilities.

Also for the judgment of the results of the treatment an exact observation can be very helpful.

I will give you a single example:

In consequence of the many different factors, which are active at home (allergic and psychological) the attacks of asthma become often so severe and so frequent, that it is not anymore possible to separate the different causes from each other.

Only as we bring the child in a favourable situation and a big part of his asthma vanishes, we keep that part of his asthma that is the most important one and that we can treat with the best chances of success

When we add to this treatment of the child a treatment of the milieu the child comes from, and where he has to return when he is dismissed, we have a good chance to reach a good result in the end.

B. STOKVIS

I completely agree with the contents of this very interesting paper. Only I should like to remark, that in our view it is not useful to treat children outside their own milieu. We prefer to treat the children psychotherapeutically, when they are in their family environment. When it is necessary to give the children a psychotherapeutic treatment in children's homes, we always combine the individual treatment with sociotherapeutical measures: group psychotherapy, play therapy in groups, psychodrama and a Punch and Judy show.

K. WILKEN-JENSEN

Fundamentally I believe that it is best to treat an asthmatic child in its usual surroundings, and I consider the sojourn in a children home as an emergency arrangement. In Denmark we can send our children to a home in Norway (in the height of about 800 m) exclusively meant for asthmatic children or to an ordinary [illegible] is especially interested [illegible] -as you may know—h[illegible] the children are free from attacks as long as they are there, but most of them relapse afterwards, some of them even have an attack in the train or on the boat on the way home. In Switzerland I was told that asthmatic children were sent to the mountains, but that the pediatricians were well aware that the symptoms recurred when the child came down again I am not convinced either that the duration of the stay in the home is of much importance [illegible]

[illegible] ot the child is more or less restored, as well specifically as totally

THE TREATMENT OF BRONCHIAL ASTHMA IN HIGH ALTITUDE CLIMATE

by

H WISSLER

It is somewhat difficult to speak about the climatic treatment of bronchial asthma because, conscious or not, the hearer suspects the speaker to talk propaganda. I understand this attitude very well. While for instance hyposensitisation or psychotherapy may be done, at least theoretically, everywhere, climatotherapy is confined to certain places and therefore experience of it is limited to a relatively small number of physicians. All I can do is to emphasize that the facts I am going to present to you have been collected as honestly as possible and according to the rules of medical science.

The high altitude treatment of bronchial asthma is time honoured. At the place where I live, i.e. Davos at an altitude of 1500 m (5000 feet), asthmatic patients have been under medical care for about 70 years. There is more than one family whose ancestors came to Davos 2 or 3 generations ago because of asthma and settled there. If we compare the first report published in 1906 with our recent studies, there is no striking difference. The experiences have been the same over the last 50 years.

According to general rules, I will first mention the facts which are well established and then the more obscure sides of the problem.

All observers agree that the majority of asthmatics are free from asthma as long as they are in the mountains. That is especially true for children. It is always amazing to hear that children have had very frequent attacks over many years at home and to see them at Davos being completely free from asthma from the first day onwards. In a study we started some years ago we found that among 200 children 85 per cent were free from asthma, while the remaining 15 per cent had only infrequent and minor attacks The 85 per cent actually had no attacks, while slight wheezing which did not hinder normal activity was not recorded. During the last years we have marked any sign of asthma, even the slightest, on our medical cards with red and even so there are many cases with no red marks at all. For the last few months we have been trying to establish clinically inapparent bronchospasms by measuring the timed vital capacity (Tiffeneau Test) before and after an epinephrine spray. It seems that this silent bronchospasm is not infrequent and is not much influenced by the climatotherapy. Yet our experience is very limited. The number of attacks depends very much on the type of cases

under observation. During the last year for instance we had a higher incidence than before. This was due to a group of English children. My English friends had collected as a test group the worst asthma cases they could find. It took several months to get them more or less free from asthma, but after a year the result was quite satisfactory.

It is unnecessary to explain to you what it means for an asthmatic child to be free from attacks. The consequences are striking, on the physical as well as on the psychological side. The weight increases, muscles become stronger, the children, often depressed and anxious, become lighthearted and more self confident. On the other hand I must mention that I never have seen a chest deformity or a marked degree of emphysema disappear. You may ask perhaps what treatment we give apart from low barometric pressure. Very little. We have breathing exercises done in the majority of cases. I think, that a prolonged siesta on the balcony is useful for most of the children. Apart from that rest period, the physical activity is normal. In summer, walks in the mountains are taken as often as possible and in winter the children go to the icerink every day. Yet we noticed that one has to be careful with these major physical exercises as many children tire very easily. As to the educational side, the children live in groups of 12—15 under the care of a trained nurse and have regular schooling in rather small classes. Psychotherapy in the strict sense is not used, but we try to increase the childrens' self-confidence wherever we can. As to the length of the cure, there are no definite rules and each case is to be considered individually. In general short cures of 1 month or so are found to be of very little use. We think that 6—12 months is generally a suitable length of time to stay.

To summarize the observations during the stay in high altitude: in almost every case there is a considerable improvement of the general condition, in the majority of cases disappearence of the clinical symptoms of asthma and in a minority only reduction of severity and frequence of the attacks.

The essential question now is, what the results will be after the children return home. The usual objection to high altitude treatment is that the results are transitory and that, a month after return, the child is in the same state as before. The question has been examined several times and the results were of a striking uniformity. So it will do if I mention a follow-up study we performed in collaboration with the university childrens' clinic at Zürich a couple of years ago covering two groups of about 100 children each, the one being treated at Davos, the other in an asthma home in the Engadin at 1800 m. The observation period varied between 1 and 6 years after return. We divided the results into 3: complete success, complete failure and between them, considerable improvement in severity and frequence of attacks. Doubtful improvement

was registred as failure. In this way we found complete recovery in 20 per cent, failure in 25 per cent and improvement in 55 per cent, or, roughly speaking, one quarter full success, one quarter failure and two quarters improvement. For the purpose of the present report, I have checked the results once more and tried to get news of the children that had left the sanatorium in the years 1949–53. The proportion was, once more, the same, the exact figures being as follows: out of the 61 cases we got answers from 12 (20 per cent) were full successes, 14 (23 per cent) failures and 35 (57 per cent) improvements.

We should like to be able to predict the result while the child is still with us. Yet, up to the present, all attempts in that direction have been unsuccessful. Our researches suggested that the failures were more frequent among children who had had eczema or among those with an allergic family history, but the difference was not statistically significant. It may be that more accurate lung function tests may give us a clue, but I feel rather that the factors which determine the final result are on the emotional side

Having mentioned certain well established facts, we have now to discuss the mechanism by which the high altitude climate acts. That will not take us long because we know very little.

First let me deal with the objection that taking asthmatic children away from home and bringing them wherever it may be can sometimes have a beneficial effect and that the so called climatotherapy is nothing more than a change of milieu. I am quite aware of the possible influence of simply separating the patient from his family and especially from his mother. Yet I have seen quite a few cases that had been brought to children's homes in the lowland without any succes but who were free from asthma at Davos. Very interesting information on this problem could be drawn from an English home at Davos, where a considerable number of asthmatic children were being treated. Many of them had spent a long time at residential open air schools in England without success and were free from asthma at Davos under very similar living and educational conditions. So we think that there must be an almost specific factor in the high altitude climate, but unfortunately we do not know what it is. The climatologic side is pretty clear thanks largely to the skilful and patient work that has been done at Davos for many years, first by Dorno and then by Morikofer. The characteristics of high altitude climate, which term is generally applied to places over 1200–1500 m., are: reduced oxygen pressure and low temperature, reduced cloudiness, especially in winter; high radiation intensity, especially in ultraviolet; reduced atmospheric humidity and almost complete absence of fog; in the valleys a good wind protection and consequently a reduced

and very regular cooling power. As to allergens, we do not know enough Pollens certainly are less and different from those in the lowland. But among my cases, pollen asthma is quite exceptional. Fungi are less frequent but are present, and our mattresses and upholstered furniture contain as much dust as elsewhere. Some information might be drawn from the effect on other allergic diseases. I had to look after a restricted number of cases of eczema. They improved considerably, but the effect was less striking than in asthma and might be due, at least partly, to careful local treatment. Among the Davos population eczema in children is rather frequent, but asthma is quite exceptional, although there are, as I mentioned, a considerable number of allergic families. It seems so, that the climate has not a general antiallergic effect but only an antiasthmatic one.

Recently some investigations have been made on the influence of high altitude on the adrenal system. Koller and his collaborators (Loeffler's clinic at Zurich) found at Jungfraujoch, 3500 m, that immediately after arrival the blood eosinophils dropped while the number of thrombocyts and the excretion of 17 ketosteroids rose. The effect was the same as that of an injection of ACTH, but it was of short duration and lasted only a few hours The same tests by the same group were done at Davos. The results were similar but less striking. Recently, by chance, another fact pointing to the same conclusions was found. Prader, children's clinic Zurich, was investigating the significance of the sodium/potassium ratio in the saliva as an indicator of adrenal function It is now clear that cortisone and ACTH depress this ratio. Prader asked me for a series of samples just for investigating children with normal metabolism and endocrinologic pattern. It turned out that the sodium/potassium ratio in our children was on an average somewhat lower than in normal children at Zurich. In order to check these results further, in a group of 20 girls who went to a camp in the mountains the saliva was examined before leaving, immediately after arrival and 10 days later. Again, a significant drop was found that persisted at least 10 days. These facts point to a possible mechanism but of course do not explain the whole of the curative effect For the present moment we have to refer, as medecine has done for centuries, to mere experience without being able to explain the pathophysiologic background

DISCUSSION

VARIATIONS OF BRONCHIAL ASTHMA UNDER THE INFLUENCE OF REGIONAL CHANGES WITHIN THE BRITISH ISLES

by

K MAUNSELL

Patients with bronchial asthma experience relief in the high mountains. Such a drastic change, however, may not be needed in all cases. It has been observed that in many instances freedom from attacks occurred within the British Isles themselves, and thus within the general framework of the British climate.

In a group of cases suffering from rhinitis, with occasional attacks of bronchial asthma, and living in Greater London, a study has been made to check the variations of attacks under the influence of regional changes, and whether or not a relation could be found between such variations and the soil of the region. The patients' histories were suggestive of the occurrence of attacks of asthma after exposure to one or multiple inhalant allergens such as house-dust, pollen and spores of fungi. Skin tests with one or several of these allergens were frequently positive The attacks both of the nose and bronchi occurred in phases, and the precipitating factors were closely linked the bronchial attacks, however, were more decisively marked than the nasal attacks Their abrupt onset, followed by periods of complete remission, impressed them on the memory of the patient. Being thus landsmarks in the patient's history, they seemed to provide evidence of the influence of regional changes on the patient The group studied consisted of 62 patients They came under observation whilst their residence was in the Greater London area Any regional change of more than a week's duration was noted, and whether or not an asthma attack occurred during this change Some changes were holidays, others were due to call-up for service in the armed forces, others permanent changes of residence Each regional change was counted, irrespective of whether it represented an area already visited by other patients. If, however, the same patient went more than once to the same area, it counted as only one regional changes, unless the patient reported that he was well on one occasion and had asthma on another, in which case these findings were regarded as cancelling each other out. The 62 patients of this group made 143 regional changes, involving 110 different places. The geological formation of these various places was checked by readings on a one-inch-to-the-mile drift map to ascertain the superficial strata.

The regional changes were divided into those in which the patients were free from attacks and those in which patients experienced attacks.

Results

1) Regional changes to alluvial areas: 35 patients, 46 areas.
   a) In 41 out of 58 regional changes, attacks occurred: 71%
   b) In 17 out of 58 regional changes, no attacks were reported: 29%

2) Regional changes to clay area: 31 patients, 34 areas
   a) In 25 out of 40 regional changes, attacks occurred 62%
   b) In 15 out of 40 regional changes, no attacks occurred: 38%
3) Regional changes to areas without alluvium or clay (mainly chalk, gravel, sand or rock) 30 patients, 30 areas.
   a) In 16 out of 35 regional changes attacks occurred: 35%
   b) In 29 out of 45 regional changes no attacks occurred 65%

TABLE I

Reaction of patients to regional changes

To:	Regional Changes	Attacks	Freedoms
Alluvium	58	41 = 71%	17 = 29%
Clay	40	25 = 62%	15 = 38%
Other Formations	45	16 = 35%	29 = 65%

Discussion

The influence of moist climatic conditions on bronchial asthma has frequently been stressed Recently Ordman (1955) reported the adverse influence on perennial bronchial asthma of climatic factors in the coastal areas of South Africa, and showed that the significant climatic factor might be the combination of high atmospheric temperature and high relative humidity in constantly narrow range throughout the day and during the year The figures presented here for a small group of cases and the variations of their asthma in various regions of the British Isles also point to the influence of the relative humidity.

The figures suggest that the [illegible] bracing and relaxing are not defined, though many people are conscious of the bracing quality of open sea, moorland and mountains According to G Manley (1953) relaxing qualities result from ground moisture combined with a high degree of humidity in the surface layers and and a lack of air movement to produce an interchange from above Such a hypothesis might well be adopted to explain the conditions prevailing in asthma precipitating areas on alluvium and clay soils These soils have a high moisture content, especially after and during rainfall. If the air is warmer above than below, and no convection currents are present, the moist packages of air rising from the ground cannot get away. If this moist still air is polluted by allergenic particles, an 'allergenic ground fog' is formed and conditions seem set for an attack. If, on the other hand, the soil

drains quickly, as in areas of chalk and sand, and low rainfall is combined with strong upward movements of air, with slight air pollution, many asthma patients find conditions for relief. In England, the Isle of Thanet, with Margate, Ramsgate and Cliftonville, seems to give the best results, and it may be that such conditions prevail on this island, with its chalk ground and comparitively low rainfall.

The exact address of each change of residence was not known, and thus the precise position of the house in which the patient stayed could not be checked. This may be of importance, for the humidity or dryness of the house in which the patient stayed might have contributed to the general adverse or favourable effect of an area

SUMMARY

The highest incidence of attacks of bronchial asthma during periods of regional [illegible] for examples, areas predominantly chalk, gravel, sand or rock in formation.

Acknowledgements

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I wish to thank Miss R. Hobling, B A. for tracing the regional changes on geological maps, which work was made possible by a grant from the Asthma Research Council.

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ASTHMA AND THERMAL SPAS*

by

P. SANGIORGI

Even in the remotest times—when a mineral spring was considered to be of divine origin and a temple was erected by its side in honour of the god who sent it and watched over it—men discovered the effectiveness ofs ome of these mineral springs in relieving a disease which they called something like 'spasm of the thorax' and which nowadays is known as bronchial asthma. Roman vestiges in Italy and Gallo-Roman vestiges in France bear witness. Besides, most medieval chronicles report on the restorative action of several, especially sulphurous springs. But it was only during the 19th century that thermal hydrotherapy got over empirism and entered the stage of clinically and scientifically tested treatment

The curative limits of thermal hydrotherapy shall be outlined presently. But before doing so, it may be as well to examine the springs actually used for the treatment of the asthma syndrome, the etiological, pathogenetic and clinical polymorphism of which is apt to extend the vast field of our therapeutical efforts more and more.

The principal anti-asthmatic mineral springs are the sulphurous, arsenous carbon gas, chloro-sodium and radio-active waters.

II

In sulphurous spas, sulphur may be present under various forms, namely: free and perfectly visible (e g the ancient Roman Aquae Albule of milky appearance); gasiform, namely represented by hydrogen sulphite with the typical bed egg smell; in the sulphide, hyposulphite or sulphate state; or even in the colloidal state. Sulphurous springs exist all over the European Continent and especially in Italy (Salice Terme, Riolo, Sirmione, Porretta, Agnano, Rome), France (Luchon, Saint-Honoré, Challes, Aix-les-Bains), Spain (Liérganes, Arechavaleta, Alham de Granada), Germany (Lippspringe) etc.

Sulphurous mineral springs supply the organism with the sulphur which, as biological chemistry reveals, has its share in the molecular structure of albuminoid bodies that in certain pathological conditions, especially in chronic inflammatory or diathesic affections come to lag in the tissue of some organs. And as we are aware that the bronchopulmonary tissue, the cartilaginous tissue, the articular and skin tissues

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contain substantial quantities of sulphur, sulphurous hydrothermal treatment is evidently efficient.

Now, do sulphurous spas exert a real anti-allergic action? We are inclined to doubt it, our own frequent laboratory tests with rabbits and guinea-pigs and those of other workers always having been negative, despite a certain, if transient desensitizing action exerted by hyposulphite, colloidal sulphur and sulphur solution, due according to Lumière and Chevrotier to the inhibitory action of the drug on the flocculation of the colloidal fraction of the blood plasma, or again to the antitoxic properties sulphur generally owns.

Sulphurous hydrotherapy was found to exert a mitigating and equilibrating effect on the neuro-vegetative system, the irritability and instability of which are the chief features of allergy in general and of asthmatic allergy in particular. Experimental and clinical tests with regard to this system in all and any of its manifestations: toning of the sluggish muscles, pharmaco-dynamic tests, oculo-cardiac reflexes, humero-tibial differential oscillometry, artery-tension, rate of sedimentation, calcemic tests, crinoreaction, endocrin disturbance, etc. clearly evidence a sedative, antispasmodic, anticatarrhal action of the sulphurous spas.

Thermal sulphur undoubtedly reduces organic combustion and develops a strong anabolic action, thus fostering glycogen synthesis and increasing the liver glycogen reserve; consequently, toning-up of the physiological liver function ensues, while so far it was seriously obstacled by an insufficiency.

Regarding direct action of sulphurous waters on the mucus of the respiratory apparatus, we do not share the opinion of those who consider this action of secondary importance as compared with the above described general effects. The Bolognese hydrology school admit local action of hydro-sulphurous inhalations, where congestive disturbances (present or past) or alterated cellular reactivity of the mucus of the respiratory apparatus permit penetration of allergens, but at the same time attribute greater importance to the anti-diathesic action than to the topic action of these waters.

There is no doubt—and ancient as well as recent clinic experience supply ample proof—that the sulphurous waters greatly favour the *local circulation of the respiratory mucus, to which the aforementioned* antiseptic, antispasmodic and anticatarrhal actions are due. Furthermore, it is a wellknown fact that the pulmonary tissue holds substantial quantities of sulphur which, however, belongs to the mucin, namely to the secretion and excretion substance of the respiratory organs; therefore, one may suppose that one of the first stages of sulphur metabolism must take place within these organs.

There is, then, the action of sulphurous spas with regard to the skin and particularly to the keratin, which accounts for their efficacy in the treatment of skin diseases that frequently accompany or follow asthma attacks They are particularly helpful in exudative and dry eczema.

Finally, the action of these very interesting and important group of spas with regard to the digestive system and biliar ducts, the female genital mucus and the renal emunctory apparatus, their anti-rheumatic, antitoxic, antiluetic, antiphlogistic actions are all apt to increase the field of their use more and more.

III

Great importance is due to the group of arsenous and arseno-carbongas spas on account of their generally known intense anti-asthmatic action, where the French spas: Mont-Dore, La Bourboule, Saint Honoré, etc. hold the first place The Mont-Dore waters are carbon gaseous bicarbonate-ferrous-arsenical, highly silica holding spas; the Bourboule thermal spring (40 to 60°) is arseno-ferrous and highly radioactive; St. Honoré spring is semi-mineral, sulphur-sodic-arsenical.

The workers who dealt with those spas (Moncorgé, Galup, Villaret, Claude Besançon and many others) have now determined the physiological action of those spas and their equilibrating action with regard to the humoral, neuro-vegetative and hormonal system of the asthmatic individual. According to this research work, a strong diathesic action is supposed to improve the constitutional complex of the asthmatic subject, or the condition of a patient affected by asthmatic disturbance, such as periodic or chronic spasmodic rhinitis, spasmodic trachitis or wet bronchitis

The action of the arseno-carbongas spas with regard to the liver is perhaps one of the most important features of the anti-asthmatic treatment, considering that bronchial asthma is nearly always accompanied by more ore less accentuated liver disturbance (in 85 per cent of the cases, according to Moncorgé, in 95 per cent according to me) and it is exactly to this more or less latent hepatism and consequent insufficient or altogether failing proteopexic function of the organ that the alteration of the humoral equilibrium in the asthmatic subject is due.

The antispasmodic action of these arsenious or arseno-carbongas waters has also been experimentally tested in the isolated bronchial muscle by exposing it to the action of an acetyl-cholinic exciter.

[illegible]

that they are not.

IV*

The chloride sodic spas with or without iodine as existing in various countries, such as Germany, Austria, Czechoslovakia and others, are undoubtedly less efficient anti-asthmatics than the sulphurous and arseno-carbongas waters. Still, on account of the action of the sodium chloride, they may be successfully applied in cases, where the respiratory disturbance appears to be caused by alterated metabolism and call —although this is not definitely tested yet—for sodium chloride springs. The iodine which sodium chloride often contains, does not exert—at least in bronchial asthma—the curative effect the pharmacological iodine owns; as a matter of fact, sodium chloride spas were sometimes found to aggravate rather than alleviate the asthmatic trouble. The cases these spas apply to shall be discussed later on

The anti-asthmatic action of some of the French and Italian spas —Lurisia Thermae being the most important—has not been tested thoroughly, in fact, their efficiency has been established theoretically, while clinical data are scarce.

As is wellknown, the essentially radioactive springs are generally poor in mineral substances and their principal action was found to be alteration of the uric acid metabolism, where their sedative effect on the central nervous system and their analgesic action on the peripheric nerves is considerable In cases of bronchial asthma of uricaemic origin, where asthma attacks alternate with gout and hemicrania attacks or with renal or liver lithiasis and which were decreed to be local colloido-clasic disorders—respiratory, articular, vascular or cutaneous—, radio-active waters really have sedative and antispasmodic and probably (now being researched) also anti-anaphylactic effect

V

It appears that only sulphurous waters and arseno-carbongas waters can be relied upon for bronchial asthma treatment, where it must be of course understood that any hydrotherapy is only an additional, if excellent and efficient treatment of bronchial asthma. Personal experience permits me to consider mineral hydrotherapy, especially the therapies based on sulphurous or arseno-carbongas spas, the asthmatic patient's most reliable ally in a battle against his disease fought with modern sedative, diathesic, specific or aspecific, dietetic and other cures.

The clinical forms of bronchial asthma calling for hydrotherapy are: pure bronchial asthma and wet asthma, be the patient young or old, be the outbreak of the disease recent or years back.

The above described physiological effects of the spas are indicative for the choice to take in the individual case: sulphurous waters apply to wet

asthma, especially to the chronic or post-bronchitis affections, where pulmonary sclerosis or bronchoectatic processes set in; they also apply to asthma of luetic origin and to asthma following skin diseases of the turpid type, to chronic colds, sinusitis and rheumatic affections.

For pure asthma of established allergic origin, sulphurous spas are effective only inasmuch these waters improve the mucus condition in the respiratory apparatus which, after thermal treatment, can delay but not prevent the allergens' attack. There are a few more advantages to be obtained with regard to the neurovegetative system, the liver and the other diathesic conditions.

In pure asthma that cannot be called allergic (and here the 19th century neurogen theory was readopted, after the exaggerated enthusiasm roused by the new allergy theories had passed) the neuro-vegetative balancing action, both vagal and sympathic, fully account for the good, if limited results, as above stated, of the sulphurous spas.

These indications also refer to the arseno-carbongas spas on account of their antispasmodic, sedative, anticatarrhal, trophic actions. These spas that, like the sulphurous spas, are not really antiallergic, cater for pure and dry asthma, spasmodic rhinitis, spasmodic tracheo-bronchitis, asthma in lymphatic, sluggish, anaemic children affected by adenoidism and tracheo-bronchial adenopathy, and for asthma complicated by cardial vascular disorder.

Regarding sodium chloride and radioactive spas that do not act direct on the respiratory system, but have a diathesic effect, it can only be said that their use is just a coadjuvant in the treatment of bronchial asthma caused by neuro-arthritic, hormonal or uricaemic affections that permit treatment with these waters in combination with sulphurous or arseno-carbongas spas. Chloride bromo-iodic spas, for instance, applied together or immediately after sulphurous spas have proved effective in many cases of asthma due to ovarian or thyroid disorders.

Hydrothermal cures are counter-advised if the 'status asthmaticus' is due to neoplasms in the respiratory system, evolving tuberculosis of the lungs, acute infectious or contagious diseases of the airways, heart diseases with insufficiency or a tendency towards insufficiency, etc.

VI

Hydrotherapy for bronchial asthma is effected in all available forms, above all inhalatory, namely: wet inhalation, dry nebulization, aerosol, humage

Inhalation introduces the mineral components of the waters direct into the respiratory apparatus with a topic effect that in many cases may be termed radical with regard to relieving chronic, sluggish, dystrophic

inflammatory disorders in any level of the respiratory system, together with sedative and antispasmodic action as numerous laboratory tests have confirmed.

Besides the topic effect of inhalatory cures, it was found that through the respiratory system general absorption takes place at a rate comparable with intravenous injections, which explains the effectiveness of mineral water inhalation in the various parts of the human organism.

Complete mineral water baths which in the treatment of asthma were rather neglected in the past, while the inhalation method was definitely preferred, gained new ground of late, as they not only proved nearly as effective as inhalation treatment, but in certain cases are even more helpful. Recent researches have, in fact, shown that the skin can absorb the principal chemicals solved in the mineral bath, so as to form a complete coating the biological action of which is obvious, considering the existing co-relation between skin and organism. Besides, during the mineral baths certain electric ionophoresic and also other phenomena arise which, however, cannot be discussed here.

The curative effects of oral administration of mineral waters or again irrigation treatment in bronchial asthma are of very scare account; still, such treatments may relieve other disorders connected with the asthmatic patient's condition

During these last few years, subaqueous clysters were experimented on a large scale, and it was found that they are almost as effective as full baths.

Hot thorax compresses, Scotch showers consisting in alternating hot and cold jets of water, hot baths subsequently cooled for 1 or 2 minutes pertain to the simple hydrology technique, and as they act by virtue of *their physical mechanism (Martinet compares them with 'vaccination* through physical agent'), they are usually applied with non-mineral water. Their relieving effect with regard to bronchial asthma is sometimes quite astonishing, as their vasomotoric action may even succeed in re-establishing the neuro-vegetative equilibrium in the asthmatic individual.

VII

Finally, there is the prophylactic action the sulphurous or arseno-carbon-gas spas can achieve in individuals who, on account of a delicate respiratory system easily contract colds or bronchitis and therefore are threatened with bronchial asthma, especially if they come from families where cases of bronchial asthma, pollinosis or other allergic affections occurred.

The writer, on the ground of his personal medical experience with the sulphurous springs at Salice Terme is of opinion that this very interesting feature of thermal hydrotherapy deserves profound study and investigation.

DISCUSSION

R. ALEMANY-VALL

Twenty years ago, I have studied (for two years together) with Dr. Claude at the thermal hospital of Mont Dore the influence of a course of waters (thermal waters) on 108 asthmatic patients.

The research of the blood eosinophiles, of the cholesterine, of the urine acid, of the oculo-cardia reflex before and after the treatment.

We were able to state the good and definite influence of this on the eosinophiles and the oculo-cardia reflex.

With some patients of Barcelona and those I have been able to observe in the hospital of Mont Dore, where I worked for several years, I have stated a good result in a great percentage of those diseases which by their clinical history and examination of allergens did not show any hyper-sensibility to a determined exterior allergy.

We think that the thermal waters of Mont Dore have an unspecific desensibilization absolutely independent of the height at which these thermal waters are situated

PREVENTING MEASURES*

by

KNUD WILKEN-JENSEN

Twenty-four years ago Rowe stated that second only to infection, allergy was the most important single etiologic agent in human symptomatology, and just as we try to prevent infective diseases it is worth while considering prevention of allergic diseases.

This problem may be approached and attacked from different viewpoints and as the first one I have chosen the genetic or hereditary influence. I am quite aware that no complete agreement exists about this question, but most authors seem to consider it a fact that asthma—or the disposition to asthma—is inherited According to Schwartz two asthmatic parents will have at least 20–25 per cent chance of having children with asthma and if one child in the family has asthma the probability will be much grater.

If only one of the parents is an asthmatic patient the percentage of asthmatic children will probably go down to about 13 per cent. But another part of the children will in both cases have other allergic manifestations.

Glaser has found 60 per cent children with 'major allergic diseases' before the age of ten. This may be taken into consideration if two asthmatic patients want to marry and plan to have children.

Ratner has disputed the significance of heredity and attached much importance to the pregnant mothers' diet. A few examples which make the sensitization in utero likely have been published but the paper by Bowen about allergy in identical twins does not give any support to this view, and it appears to me to be rather doubtful

The next point is the elimination By this I do not mean the elimination diet which we heard about yesterday, but a potentially allergic child may be protected against several allergens thus avoiding the possibility of being sensitized. The child must be immunized against the different childhood infections because experience tells us that they may act as the initiating or aggravating mechanism, and great care must be taken to avoid exposure to especially pertussis as this seems to be the worst of the common infections. It is especially important to immunize against tetanus as the tetanus antitoxin usually is made from horse serum which may be dangerous to the patient. If an asthmatic or potentially asthmatic patient has been infected, antibiotics should be administered

* From the Out-Patient Clinic for Children with Allergic Diseases, Rigshospitalet, Copenhagen

to a greater extent than usual, but it may be of value to vary the remedy in order to avoid drug allergy.

An important thing is—as you all know—toc onsider the environment of the asthmatic or potentially asthmatic patient. The bedroom should contain as little furniture as possible and especially have as few dust collecting things as possible. The bed should have no ordinary mattresses or pillows unless these are enclosed in dust-proof plastic casings. But it is perhaps wiser to use sponge rubber, or the mattress may be filled with paper in small bits; the cover can be woollen blankets which must be washed frequently and the pillow may be replaced by a great towel in the casing so that they can be washed too. Anything with feathers and silk must be abolished, and of course no animal pets are allowed, at least if the allergy is of a disabling type.

With regard to food Glaser postulates that it is of value to give babies in allergic families soybean milk instead of cow's milk if the mother cannot or will not nurse her baby. He claims that a far smaller part of the soybean milk fed babies developed an allergic disease than the controls. His paper seems to be the only one published of this kind.

I do not intend to give you all the details of the way in which a child's or perhaps rather an infant's diet should be varied and altered according to reactions and age, but only mention that any new kind of food should be given in small and gradually increasing amounts

But another thing is that it is often unwise to force a child to eat some food which it does not like as it often seems to be a kind of food to which it is reacting if tested

Speaking about elimination it may be worth while mentioning the advantage of occupational guidance before entering a profession

I do not believe in the value of so-called hardening processes as cold showers, diving into cold water and sleeping in cold rooms, nor do I consider the different systems of respiration exercises as being of any great importance.

I have tried to let some of my patients learn respiration exercises and some others to learn relaxation exercises but only very few seemed to benefit from it and I wonder if these treatments are of more than psychological significance.

By this I do not want to indicate that I underestimate the significance of the psychological side of the prevention. Quite on the contrary, I look upon it as very important. I always teach parents and relatives to the patients to treat them as normal healthy individuals but of course without forgetting their individual hypersensitiveness The more they are surrounded by fear, overprotection and prohibitions the more the patients feel themselves abnormal, weak and second-class persons, and the more attacks do they develop. If a patient is warned against doing

one thing or another he will not be certain that he could not endure it, but if he is allowed to try and fails he is convinced and likely to try much more to get rid of his weakness. Away from the usual surroundings patients will often stand many physical exertions which would be impossible at home in the asthma-minded atmosphere. So if it is possible to lessen the tension, the aggression and the anxiety of the family all the psychologically provoked attacks may be abolished.

If a patient knows that he has to go to a place where he is likely to develop an asthmatic attack he may be able to prevent it by taking one of the many antihistaminic drugs but their effect is rather unreliable in asthma.

In other cases he may be protected by taking ephedrine 3—4 times during the day or a prescription which we use very much instead of pure ephedrine as it seems to be tolerated better and have the same effect. It consists of:

Phenacetin	
Theophyllin $\overline{aa}$	ctg. 5
Coffein	mgm. 25
Ephedrine hcl.	
Extr belladonn. $\overline{aa}$	mgm. 5
Agaricin	mgm. 1,25

PSYCHOTHERAPY IN ALLERGIC PATIENTS*

by

B. STOKVIS AND A. J. WELMAN

A) INTRODUCTION

When we speak of psychological therapy, or better still of psychotherapy, for those who suffer from allergic disturbances, we postulate that in fact no differences exist between the various forms of therapy; that we are dealing with therapy as such. Still the human being, and thus also the sick individual, should be considered as a 'mind-matter' entity—a *psychophysical totality with a free mind.*

The mental need in which a sick person finds himself must not be underestimated—regardless of whether the illness be determined predominantly by mental, or by somatic conditions—such an individual is still a person-in-distress.

This concept is, in fact, already expressed in the suggestive manner in which even the non-psychologically oriented physician administers medicine—each medicament having, in addition to its pharmaco-dynamic action, a psycho-dynamic one. The latter is dependent not only upon the nature of the drug and the method of administration, but also upon the particular relationship that exists between the doctor and the patient—the so-called transferance situation.

Psychotherapy is an attempt to psychically influence the sick individual—that structured, living totality with a free mind. Its purpose is to cure, or in a given case, to relieve or actively control the suffering

While psychotherapy was originally almost exclusively directed toward patients with mental disturbances, during the last ten or fifteen years the indications for psychotherapy have broadened. Those diseases which previously were considered as exclusively somatic, the so-called psychosomatic disturbances, also belong to the indication sphere of psychotherapy.

At the Leyden Psychosomatic Center, we include under psychosomatic disturbances all diseases which are expressed in the bodily sphere and for the appearance of which emotional factors in the present or past are responsible. Utilizing this broad definition, it is no longer necessary to limit the concept of psychosomatics to the complex of psychosocial diseases such as Asthma, Ulcer, Colitis, Anorexia nervosa, Coronary Artery disturbances, Migraines and Hyperthyroidism—as did

* From the *Psychosomatic Center*, State University, Leyden.

Halliday.[26] These diseases we group under the collective title of 'Somato-Neuroses'—this in contra-distinction to 'psycho-neuroses' (neurotic phenomena in which mental disturbance is noted). In addition to the somato-neuroses, we distinguish somato-psychoses (psychotic disturbances which are expressed in the bodily sphere). Moreover, we also consider conversion-hysterical reaction forms, organ neuroses and vegetative neuroses in the same group as psychosomatic diseases (namely, somato-neuroses). Patients with chronic somatic diseases to which they react in a neurotic manner, are also entitled to psychotherapy and, for that reason, are considered as having a more or less psychosomatic disturbance.

I. NEUROSES
  A) *Psycho-Neuroses*
    1) Hysterical Neuroses (among others, conversion-hysterical reaction forms).
    2) Compulsive Neuroses.
    3) Neurasthenic Reactionforms
  B) *Somato-Neuroses*
    1) Psychosocial diseases (so-called psychosomatic disturbances sensu strictiori).
    2) Organ Neuroses.
    3) Conversion-Hysterical Reactionforms.
    4) Vegetative neuroses.

II. PSYCHOSES
  a) Psychoses sensu strictiori.
  b) Somato-psychoses.

III. SOMATIC DISTURBANCES (neurotic reaction to chronic disease).

IV. NERVOSITY (constitutional disturbance with vegetative phenomena).

Application of psychotherapy to psychosomatic disturbances in the broad sense of the term, is aimed at treating the emotional determinants which condition the somatic illness. Lately, the attempt is being made, not only to influence the affective factors, but at the same time to reach the sick individual himself—to subject his place in the world to closer scrutiny (von Gebsattel,[22] Caruso,[11] Frankl[20]).

In psychotherapy as in somatotherapy, a scientifically justified set of indications is indispensable.

This set of indications for therapy is dependent on three factors: the nature of the disease, the personality structure of the patient and that of the doctor. While choice of therapy in somatic disturbances is decided by the nature of the illness, in psychotherapy, the decision depends upon

the personality structure of the patient and of the doctor. In order to learn the patient's structure, we utilize structure-analysis with the aid of psycho-diagnostic investigation. For this purpose, the results of the tests are arranged in terms of the five facets of personality, as described by Carp [9] (Drives and Temperament as biological basis, intelligence and psychomotor, with character as keystone). In our Psychosomatic Center, we use the following battery of tests routinely. the Wechsler-Bellevue test; the Rorschach test; the Szondi test; the Thematic-Apperception test; the Four-Picture-Test; Wartegg test and the House-Tree-Person test

The indication for psychotherapy in psychosomatic diseases depends on the results of the psychosomatic investigation as a whole—in other words, it depends on the results of the biographical, the psychohygienic, the physiopsychological, the socio-psychological, the psychiatric and last but certainly not least, the somatic investigations

B) PSYCHOTHERAPEUTIC METHODS

We will now briefly elucidate some of the psychotherapeutic methods These are broken down into individual treatment methods and methods whereby the patients are treated in a group.

The methods of treating the individual consist of the covering (non-exploratory) and the uncovering methods as well as the psychagogical methods (see table 2). In the covering methods, the psychic factors which condition the disease are not sought—these actually being pushed still deeper (into the unconscious) (repressed). The uncovering methods pre-suppose a causal-etiological therapy. The factor causing the illness is here unearthed, is interpreted and, thanks to the enlightened insight that the patient obtains, the damaging action of the earlier psycho-traumatic event is eliminated. In the psychagogical method, the patient is shown how best to direct and lead his future life

The covering methods utilize suggestion and auto-suggestion—while hypnosis acts as a bridge between the covering and uncovering methods. The uncovering methods include hypno-catharsis, narco-analysis (drug-psychotherapy) in addition to the methods of Freud, Jung and Adler.

Psychagogic treatment can be administered as a re-education. This requires self-education, though suggestion can also be utilized. For this purpose, behavior patterns are drummed into the patient's head.

In group therapy, mutual exchanging of ideas between patients is encouraged (group discussion), moreover, the varying attitudes of patients executing a joint work project is utilized (activity groups). It is also possible to study the reactions of the patients during a popular lecture (didactic groups) In the psychotherapy depicted, psycho-drama and finger-painting are chosen as starting points for emotional expression.

In this connection, we must also include socio-therapy, which acts to stimulate a feeling of responsibility in a community of patients (Carp,[10] Daumézon,[14, 15, 16] Sivadon[63, 64, 65]).

Case-work, whereby the social worker helps with the therapeutic difficulties, deserves separate mention. In 1922, Mary Richmond gave the following description of this: 'Processes which develop personality through adjustments consciously effected, individual by individual, between men and their social environment'.

In 1953, the Commission for Social Hospital work, defined case-work in the following manner: 'The aim of case work is to study the social (personality and environment) factors in the life of the patient, in conjunction with the doctors concerned, in order to obtain insight into the connection between the development and course of the disease, and in addition, to attempt to alter these social factors in order to promote recovery and to prevent relapse'.

Naturally, social therapy is important in the treatment of psychosocial diseases.

Before discussing our own experiences with psychotherapy in asthmatic patients, we shall first summarize the pertinent literature. *

C) SURVEY OF THE LITERATURE CONCERNING PSYCHOTHERAPY IN ASTHMA

This literature has, by this time, become very extensive; the different authors seem to prefer diverse psychotherapeutic methods. Many investigators use the word 'psychotherapy' in general, without precisely describing the method used. Most publications scarcely mention any figures. It is noteworthy that in important clinical works on asthma such as that of Cooke, Feinberg,[19] Hansel,[27] Vaughan,[77] little or no mention is made of psychotherapy. We shall try, in so far as possible, to arrange these literary excerpts according to the forms of psychotherapy employed.

I. THE SIGNIFICANCE OF PSYCHOTHERAPY IN GENERAL

Long ago, Hippocrates[31] discerned a connection between bronchial asthma and emotions and made use of this connection in his treatment of this condition. Also, several 7th. century commentaries discuss the importance of psychotherapy in bronchial asthma. Two 17th. century authors, Henry Hyde Salter[57] and John C. Thorowgood,[74] pointed out in their own ways, how a conversation could act as a curative agent.

* The connection between the mind and allergy in addition to the psychological aspect of bronchial asthma need not be discussed here. The literature on this subject is extensive.

F. Reichmann [53] (1922) described bronchial asthma as a neurosis on a psychopathic base. She deems psychotherapy the mainstay of the treatment—with drugs as an eventual adjunct. She is concerned with the 'how' and not the 'what' in the treatment of asthmatics.

E. Moos [46] (1923) discusses seven patients who were cured with psychotherapy where somatotherapy had failed. Those patients whose sputum previously had contained Curschmann's spirals and Charcot-Leyden crystals, now had sputum which was negative for these. In two cases, approximately 200 cc. of sputum were produced daily—this symptom also disappeared completely. The eosinophilic blood picture returned to normal. In a later article (1928) [47] he describes 16 patients with definite somatic symptoms who were cured.

Using psychotherapy, J. Loewenstein, [37] (1926) noted a definite improvement or cure of 60—70 per cent of a group of 48 asthma patients. Among other things, he pointed out the importance of the psychoanalytic method.

Psychotherapy is also considered of great importance in bronchial asthma by C. Romer and A. Kleemann [55] (1927). They describe 10 patients with extensive somatic symptomology who reacted favorably to psychotherapy whereas somatotherapy had had little or no success. One patient showed a decrease from 24 per cent to 4 per cent in eosinophil cells in the peripheral blood.

Pollnow, Petrow and Wittkower [51] (1929), as a result of their experiences with 45 patients, prefer psychotherapy. They chose a therapy giving insight in preference to hypnosis because the former method is more causally directed.

Other authors who recognize the importance of psychotherapy are Gottlieb, [23] Kronfeld, [34] F. Mohr [43] and Unger. [76] Mohr, in a later publication [44] (1949) [45] (1954), points up the significance of an analytic aspect in this therapy.

E. G. Billings [6] (1947) discusses the treatment of 17 cases of 'psychogenic asthma'. He was successful in 6 of these cases—but does not indicate the method he used.

Further more, Freuting and Ripley [21] (1948) discuss the use of both somatic and psychic therapy in a number of patients. The group of 24 who received psychotherapy over periods of time ranging from several months to 2 years responded most satisfactorily of all In one instance, hypnosis was used with good result.

In Holland, Van Lookeren Campagne [38] (1950) and Quarles van Ufford [52] (1950), and others, stress the importance of psychotherapy —especially in children. The former points out that while such treatment is important for curing asthma bronchial qua talis, it is, in addition, important for the development of the child's personality.

Various authors consider the combination of allergic and psychotherapeutic treatment of value. Abrahamson[2] (1951), E. A. Brown[8] (1951), E. Weiss[78] (1950), Groen[25] and others use a combined treatment of ACTH and psychic influence.

II. THE SIGNIFICANCE OF UNCOVERING METHODS OF TREATMENT:
We can divide this methods into 4 groups:

1) *Psychoanalysis*

In his publications[28] (1927), [29, 30] (1929), [31] (1930), Hansen appears to be very critical of the value of psychotherapy. Still he considers psychotherapy necessary in a number of cases. He feels, however, that only the analytical method is important. He considers hypnosis as less desirable. Abrahamson[1] (1948) discusses a number of patients who reacted favorably to psychoanalysis. In the Netherlands, Bastiaans[5] *also used the psychoanalytic method on a number of patients*—and furthermore, considers the so-called short therapy useful in asthmatics.

2) *The Short Therapy*

This method was introduced by Alexander[4, 3] and French[3].

It gives the patient an opportunity at catharsis in several sessions. The patient is given insight into his problems through analytical means. Levine[30] (1952) describes a boy who lived in an iron lung and could not dispense with it for more than 3 to 5 minutes at one time. This, however, did not agree with the somatic condition. After a short conversation, an anxiety element was uncovered and the boy was able to remain out of the iron lung for an entire day. One of us[67] (1953) discussed a 51 year old patient who had suffered from bronchial asthma for 15 years Using a short psychotherapy in the form of a combination of insight, uncovering and cathartic treatment together with relaxation therapy (Active relaxation), we obtained good results with this patient. Zoss[79] describes a patient in whom an anxiety situation cleared up in three sessions.

3) *Catharsis*

Some writers indicate that catharsis alone can work therapeutically. Experience has shown even the non-psychotherapeutists how the relating of one's life history can work to relieve tensions. This fact was pointed out by Naber[49] in 1929 and again by Miller[39] and Skands[66] in 1951.

In this connection, the 'non-directive psychotherapy' of Rogers[54] can be mentioned. Mitchel[41] (1946) and, later, Mitchel[42] Curran and Meyers (1947) treated a number of patients using this method with good results. A special form of catharsis is that brought about under the influence of hypnosis or 'drugs' (the so-called drug psychotherapy). This method was described by Cohen[12] (1946—The narcoanalysis of 2 women).

4. *Other Methods*
In our Psychosomatic Center, we use other uncovering methods when indicated. These include the individual psychologic method of Adler and the psychagogic treatment of Kronfeld.[34]

III. THE SIGNIFICANCE OF THE COVERING METHODS OF TREATMENT

1) *Autogenic Training*
I. H. Schultz,[58, 61] the initiator of this method, has this to say about it: 'Es ist dies die übende Erlebung einer Selbstumschaltung, die sich durch bewusste Zuwendung auf das Endosensorische bei Aussenreizverarmung, Immobilisation mit Entspannung systematisch entwickelt'. Schwoebel[62] (1948) noted an average increase of 500 cc. in vital capacity using this method (combined with massage and with breathing excercises). He obtained good results in 42 of 50 patients. Trautwein[75] treated 40 patients with this training and obtained distinct improvement in 95 per cent. In 50 per cent the asthma disappeared completely. Many other investigators have obtained good results with:

2) *Hypnosis*
One of us[69, 70] has had favorable experiences using hypnosis in asthmatics. Schultz[59, 60] obtained favorable results with asthmatics whose sputum contained Curschmann's spirals. In 1910, Brügelmann[7] described this method. Laudenheimer[35] successfully combined this method with breathing excercises in 1926. Flanders Dunbar[18] described a patient of Costa's in her book. Despite serious somatic symptoms, this patient was cured.

3) *Relaxation Therapies*
Groen[24] (1946), Ross[56] and Wilson and others described the significance of these methods. They emphasize the significance of crying in the treatment of asthmatics: '.... and the relaxation of their ability to do so in psychotherapy is frequently followed by great relief of symptoms'.

4) *Suggestion*
This also has important therapeutic significance. Tagerberg[73] (1953) describes how he substituted physiologic saline injections for ACTH in patients requiring ACTH and still obtained the same subjective results. (Somatic symptoms, such as râles and eosinophilia remained unchanged). Dees[17] also stressed the significance of suggestive factors.

5) Finally, *Mechanization* has made its appearance in psychotherapy. Morwood[49] makes use of a gramophone in asthma. A method of inducing a state of semi-hypnosis by a formula of words given by gramaphone. Naturally, this method is a modification of the suggestive —autosuggestive method.

As the last group of therapy, we turn our attention to:

IV. THE SIGNIFICANCE OF GROUP PSYCHOTHERAPY
Miller and Baruch [40] discuss the favorable results obtained in several asthmatics using group treatment. Groen, [25] also, obtained results with this method.

D) OUR EXPERIENCES WITH PSYCHOTHERAPY IN ASTHMATICS

The following is an account of our experiences in the Leyden Psychosomatic Center. [70, 71] We are here concerned with 80 asthmatic patients who were examined by us since the establishment of the Center in January 1952. Of these, psychotherapy has thus far been used in 30 cases.

Following the methods and theories advocated in our Center, we treated the patients with either the uncovering or the covering methods. From the first group, we selected cathartic-analysis, the short therapy, and where indicated, the method of Adler. In spite of being convinced of the supreme place occupied by Freud's psychoanalysis in many cases, we were thus far forced to abandon a systematic application of it, due to varied circumstances. Hypno-catharsis was used in several cases where an actual conflict situation existed and where connected affective tension was present.

Of the covering methods, we used hypnosis and relaxation therapy on asthmatics in our Center. Of the various relaxation methods, we used Schultz's autogenic training and also active tonus regulation—which is customarily used in our Center. Naturally, suggestion in the form of administration of placebos was used in many cases. Recently, Pflanz [50] formulated an important explanation of this form of 'pharmacopsychology'. In diverse cases, the psychagogic treatment was used in order to present the patients with aspects and perspectives of life. Where the intelligence was insufficient, it was necessary to abandon re-education in the sense of self-education, and utilize suggestive or even hypnotic methods (Kretschmer) [33] in order to accomplish re-education.

In addition to the individual treatment, 40 per cent of our asthma patients were treated with group therapy—group discussion and psycho- and socio-drama were the forms of group therapy used.

Those patients admitted to the hospital were, in addition, treated socio-therapeutically in conformance with the newer points of view (see Carp, [10] Daumézon [14, 15, 16] Sivadon, [63, 64, 65]). In socio-therapy, an appeal is directed at being responsible to each other and for one another. Further more, attempts are made to extract the patients from a fettered relationship in which there is a feeling of dependence upon one another and to supplant this with an associative relationship based on attachment to one another. In order to bring this about, the so-called Patronage Principle of Carp [10] is employed.

TABLE 1

Psychosomatic diseases viewed pathopsychologically

I NEUROSES
- a) *Psycho-neuroses*
  1. Hysterical neuroses (incl. conversion-hysterical reactionforms)
  2. Compulsion neuroses
  3. Neurasthenic reactionforms
- b) *Somato-neuroses*
  1. Psychosocial diseases
  2. Organneuroses
  3. Conversion hysterical reactionforms
  4. Vegetative neuroses

II. PSYCHOSES
- a) *Psychoses (sensu strictiori)*
- b) *Somato-psychoses*

III CHRONIC SOMATIC AFFECTIONS
with neurotic complication

IV. NERVOSITY
constitutional disease with vegetative symptoms

TABLE 2

Psychotherapy applied in asthma patients

I. *Individually applied*
- a) Covering Psychotherapy
  - Suggestive Methods
  - Auto-suggestive Methods (relaxation)
  - Hypnosis
- b) Discovering Psychotherapy
  - Hypno-catharsis
  - Narco-analysis
  - Psycho-analysis (Freud)
  - Individual Psychology (Adler)
  - Complex-Psychology (Jung)
- c) Psychagogic Psychotherapy
  - Re-education (Kronfeld)
  - Suggestive-psychagogic

II. *Groupswise applied*
- a) Discussion therapy
- b) Activity group
- c) Didactic group
- d) Psycho-drama, Finger-painting

In many cases, finger-painting is used by way of experiment as an expressive form of psychotherapy. This treatment acts to relieve tensions and the drawings sometimes offer the therapeutist important clues in support of the individually applied uncovering therapy.

In conclusion, we shall present the results of the various treatments used. The criteria suggested by Groen[25] and Orie were used in judging our results. These include: subjectively perceptible wheezes, objective symptoms and complaints of the patient. In most cases (66 per cent), a combination of psychotherapy and somatotherapy were employed. As the psychotherapy made progress, the somatic treatment was gradually decreased. The results can be summarized as follows:

Using uncovering treatment, all the patients showed some improvement and with covering therapy, 85 per cent of the patients improved.

TABLE 3

Results psychotherapy bronchial asthma patients

Form of psychotherapy applied								Degree of improvement		
Individually						Groupswise				
Discovering (13)		Covering (11)		Psychagogic (6)		Discussion Psycho-Drama (13)		Complaints	Subjective wheezing	Objective findings
No	%*	No.	%*	No.	%*	No	%*			
2		4		3		1		—	—	—
5		2		1		6		—	—	slight
2		2		2		2		slight	—	wheezing
4		3		-		4		rising	wheezing	wheezing
-		-		-		-		non-rising	Status asthmaticus	

* Number of patients too small.

A catamnestic investigation revealed, of those that responded, that the improvement, in most of the cases, remained constant. The control time varied between ½ and 3 years.

It is interesting to compare these results with those obtained by one of us employing psycho-therapy in psychoneurotic patients[68]. When one bears in mind that asthmatics are, in essence, patients with somatoneuroses, one will not be surprised that the respective results are more or less similar.

Our conclusions indicate that, in the light of present day opinion, application of psycho-therapy to bronchial asthma sufferers must always be considered. Let us hope that, with this consideration as starting-point, we shall be able, in the near future, to completely bridge the old, unjustifiable gap between allergologists and psycho-therapeutists. We must not forget: the object of this address is and remains the human being, who, due to the Cartesian Teaching of diaschizis, has for centuries been unjustly separated into body and mind In accordance with our present day opinions on that subject, he is a psychosomatic totality—and, as such, when sick, deserves to be psychosomatically treated

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DISCUSSION

D. LEIGH

In any consideration of the psychological aspects of asthma, sound scientific methods must be used.

A brief résumé of a statistical study of the psychiatric symptoms found in asthmatic patients with adequate control material reveals some interesting findings. In order to avoid the criticism that asthmatics who attend a psychiatrist differ in some way from asthmatics who attend a general physician, a control group of asthmatics attending a general physician was compared with a group of asthmatics attending a psychiatrist. Two further control groups were used; a group of neurotic patients and a group of normals.

Using Student's t. test it was possible to show that there was little significant difference between female asthmatics attending a general physician and those attending a psychiatrist. There was a marked difference, however, in the male population Men who attended a psychiatrist were very much more disturbed psychiatrically than those attending the physician. When compared with normals and neurotics the asthmatics were seen to fall somewhere between the two in their particular ratings

These findings are being extended and amplified as they have considerable theoretical interest, both aetiologically and therapeutically. The main purpose, however, of this brief communication is to put forward a plea for the use of sound statistical and scientific methods in the study of the psychological aspects of asthma.

P. J VAN DER WERFF

I do not agree with the view that psychosomatic medicine is a modern branch of science, since it is as old as the history of mankind. We realize this, when we see the pictures in caves, made by prehistoric men, especially those in Spain, or when we see, read or hear about the medicine men of recently discovered primitive tribes in Western Australia, Mid-West Africa or the virginal forests of South America; one of the differences in methods being, that these witch-doctors spoke and speak through wooden tubes and not on the radio, such as sometimes occurs nowadays.

The good general practitioner of to-day, who is the faithful friend of the family, and the specialist, who does not treat 'cases' but human beings with somatic disturbances and diseases, are also practising genuine psychosomatic therapy every day.

Therefore, apart from allergenic factors, bacterial infections in the respiratory tract and elsewhere in the body, endocrine disturbances etc., and now only in regard to psychogenic factors what makes us, allergists, reluctant are several principles of certain psychosomatic work-teams, for we do not deny the importance of the psychological factors. We hesitate to accept the principle of the specificity of the personality structure and of the specific conflict situations of psycho-

somatic patients in general and of patients with asthma in particular, as we see all kinds of neurotic reactions, mental disturbances and all kinds of personality structures in our patients with bronchial asthma as well as in those with colitis or with combinations of these and other allergic syndromes. Although I cannot agree with their points of view, on the other hand I do agree with the views I heard to-day from the mouth of Dr. Stokvis, as a representative of the Leyden School [illegible]d, as it was beyond [illegible] Meeting).

[illegible]

1) What is your opinion on the question of primary or secondary psychogenic asthma?
2) When you assume the existence of both: i e. a primary and a secondary psychogenic origin, does this make any difference to your psychotherapy?

My questions are based on a case (which you perhaps remember yourself) of a man of about 45, no known allergies in the family, with only a slight allergy to inhalants and foods. He was unable to do any work due to a characteristic bronchial asthma He was 6 months old when his mother died; he was brought up by an aunt; shortly after he had his first attack of asthma Is it possible, that here we were concerned with a patient as has been described by Alexander, affected with a primary psychogenic asthma?

K. WILKEN-JENSEN

Unfortunately the paper of the relator was quite different from what I expected and it contained so many fine psychiatric expressions which I do not know that I cannot enter into any discussion with him

In spite of that I would like to mention that a few years ago a specialist in [illegible]

tric Congress in Stockholm but have only been printed as a summary. I shall not go into details about the investigation, the results of which were compared by means of cards with a system of holes. The psychologic differences between the groups were only small, especially between the allergic and the 'neurotic' group, the only difference of real importance being that the allergic children were more anxious, and this anxiety may even be secondary to the asthmatic attacks so that the asthma has caused the anxiety. A special psychologic type was absolutely not to be found in the allergic group

E. WOLFER-BIANCHI

In my opinion we are speaking nowadays too much of psychologic factors in the origin of asthma and the need of psychological treatment. In several thousand cases of asthma the probable psychical origin was stated only in one patient.

In a minimum of 20 cases would impede the results of our ts to a psychotherapeutic specialist a good result by hypnosis. The asthma should not be called a psychosomatic disease, it is a somatic one in clinical and anatomical view and should be treated with our clinical methods. In each disease we find psychological troubles. It is the task of the physician treating asthmatic patients to look after their psychical conditions and troubles and to help them by the simple methods of the so called, 'short psycho-therapy'.

REPLIES

by

B STOKVIS and A. J. WELMAN

to J. F. Farrerons-Có

We have had the same experience as Dr Farrerons.

There is a certain risk of losing a patient who refuses to accept the suggestion of consulting a psychiatrist At our Center we dealt with this problem by inviting the internist personally to introduce the psychotherapist to the patient It is on the manner in which this first contact is established that the success or failure of the subsequent psychotherapy depends.

to D Leigh

We should like to stress the fact, that we quite agree with Dr Leigh in principle. We tried to make it quite clear in our paper that control material (catamnestic examination) is indispensable for judging the results of the psychotherapy. We have followed up our patients for periods between six months and three years. For this reason we have discussed only thirty patients out of the eighty we have so far treated psychotherapeutically in our Center. That is why we preferred to avoid any pseudo-accuracy by not presenting statistical data. Moreover, we did make a comparison between the psychotherapeutic results in asthmatics (somato-neurotics) and those in psycho-neurotics. We may conclude, therefore, that Dr. Leigh's views and our own are, in essence, very similar.

to E Wolfer-Bianchi

We quite agree that, in many cases, the psychic component of the asthmatic trouble appears hardly perceptible. We therefore invariably make, at our Center, in every case of asthma, a psycho-diagnostic examination. Only in this way one can reveal the actual presence of the psychic factor.

to P. J. van der Werff

Yes, we are, in fact, of the opinion that there exist both primary and secondary

psychogenic asthma, although it is not always an easy matter to decide which is which in a given case. The somato-allergic determinants and the purely psychic ones are very often inextricably mixed up. Moreover, these factors influence each other mutually.

Secondary psychogenic asthma is exceedingly frequent, on account of the almost invariable neurotic way in which the patient experiences his state of chronic illness. In addition, there is the frequent action of some conditioned reflex, even in those cases where the neurotic complication is not present

I wonder, whether the case to which Dr. Van der Werff refers, was a case of primary psychogenic asthma, with subsequent somatic allergy to inhalants and foodstuffs Of course we do not know anything of the earlier contact of the patient—when he was a baby—with allergenic factors, e g. house dust etc.

In this respect Dr. Welman and I want to emphasize that—in our opinion—psychosomatic factors should be distinguished into:

1) psychic
2) somatic } factors
3) social

In our Center we always try to investigate these three factors together in every separate case, and we definitely give our full attention especially to the *somatic* [illegible]

We do not agree with the monocausative aetiological theory.

With regard to Dr Van der Werff's second question, the presence of either primary or secondary psychogenic asthma makes no difference to the therapy.

I may perhaps add that the Leyden Psychosomatic Center does not adhere to the principle of specificity with respect to the personality structure and conflict situations of psychosomatic patients in general, and of asthma patients in particular

Dr. Van der Werff's questions appear to me of essential importance, because, if my explanation is correct, the bone of contention between allergologists and early psychiatrists thereby vanishes into thin air.

to K. Wilken-Jensen

We are very pleased to note that Dr. Wilken-Jensen had the same experiences in making his very interesting psychological experiments as ourselves. We should like to thank him for his statement to that effect.

to R. S Bruce Pearson

This is a very important question. In psycho-therapy, too, we have our sharp [illegible] rsonality struc- [illegible]; psychotherapy [illegible] part. Covering

methods (suggestion and auto-suggestion) may be used in all cases. Middle-aged patients should be induced to resign themselves to accepting the fact of their illness. For these patients, analysis is contra-indicated, owing to the lack of integrative possibilities. Whenever possible we give them some insight into their life's problems ('short' psychotherapy of Alexander and French); and failing this, an (auto) suggestive or suggestive-psychological treatment.

BREATHING EXERCISES AND GENERAL GYMNASTICS IN PATIENTS WITH BRONCHIAL ASTHMA *

by

W. J. QUARLES VAN UFFORD

The dyspnoea associated with asthma is due to spasm of the smooth muscle tissue of the bronchioles, obstruction of these air passages by viscid mucus or rapids welling of the mucosa. In each of these three cases the result will be identical, viz. the alveolar air is expired with great difficulty. This is due to the constriction of the respiratory tract; inspiration, but *especially expiration*, has become difficult and this results in dilatation of the alveoli and depression of the diaphragma.

All muscles are in action, the normal muscles of respiration, the accessory muscles of respiration of the shoulder, neck and even those of the nose.

In terms of physiology: the residual volume has increased (e.g to 40 p[illegible]
the v[illegible]
decr[illegible]
'first second value' we mean the percentage of vital capacity that can be expired in one second after an inspiration of maximum depth, followed by an expiration of maximum depth and maximum speed.

This percentage is also called the *utilizable portion of the vital capacity*, as it shows what portion of the vital capacity can be utilized.

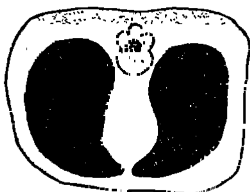
Bronchial asthma, in which the expiratory phase is prolonged, is marked by a diminished first second value. Thus the percentage may be 50 per cent instead of the normal 70 per cent—85 per cent of vital capacity.

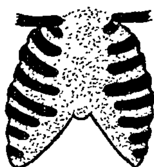
Pulmonary function tests following the injection of adrenaline show a considerable improvement of the respiratory curve This is of particular importance in determining the degree to which the changes in asthma are reversible.

We shall examine the effect of attacks of dyspnoea on the body and the extent to which physical therapy may be used in *prevention* and *treatment*. The great advantage of this method of treatment is that the patient is provided with a weapon, which he can use at will. We look with horror upon the abuse of pocket inhalers (of which the patient carries as many as 2 or 3 with him, if possible).

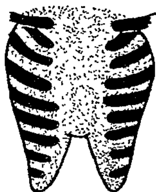
The purpose of postural and breathing therapy is not only to teach the patient what to do in case of emergency, but also to improve and to prevent.

*From the Allergic Department of the Diaconessenhuis, Utrecht (Dir Dr. M. A. VAN MELLE).









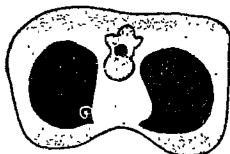


Fig 1



Fig 2

Let us imagine ourselves in the position of our asthmatic patient with chronic dyspnoea. Let us give a moment's thought to his thoracic deformities, his typical posture, in which the chest moves rapidly up and down, let us bear in mind his dyspnoea on any exertion, his tense posture, his anxiety.

We shall examine what can be done on these fronts:
1) correction of posture
2) breathing exercises
3) improvement of the resistance of the patient
4) relaxing exercises.

Chronic asthma results in changes of the thorax, the nature of these changes depending on the age of onset of the attacks of asthma. (fig. 1—7).

In infants 'the give' takes place at the cartilages on each side of the sternum. This bone is sucked inwards and may remain a deep concavity throughout life.

In children the chest assumes the pigeon breast type, with the enlargement at the lower part of the chest, not the upper.

In older subjects the bone cage is fully hardened and worked by strong muscles, the result being the formation of the barrel-shaped chest and the production of emphysema

It is the object of breathing exercises and postural therapy:

1) to prevent and possibly improve the anatomical changes caused by the attacks of bronchial asthma.

We shall illustrate this statement by the following example. When children are ordered to 'sit smartly' in elementary schools in this country, they have to sit with their arms folded in front of them on the school-desk. This position results in forward displacement of the shoulders. As it is, patients with asthma are conspicuous for their stooped, drooping shoulders Accordingly this would be promoted by the position of the children at school if they were not ordered to fold their hands behind their backs when 'sitting smartly', so that the shoulders are drawn backwards.

This correction of posture is also obtained by swimming, which also is an excellent form of breathing exercise.

I do not believe that the question what exercises are most suitable for a patient, Swedish gymnastics, the French system, the Mensendieck system, or whatever they may be called, is the most important feature (fig. 8—9). We must picture to ourselves how deformities of the chest, dependent on his age and symptoms, will occur in a patient with asthma and examine the best method by which to treat these changes in this case.

To a large extent, this will also depend on the patient. It is foolish to determine in advance, that all patients should in all conditions be

treated in accordance with a fixed scheme of treatment. The physician should first ask himself the question, what changes may be expected to occur in the chest and therefore how to treat these changes in the first place. Horizontal bars will be an excellent apparatus in some cases, morning and evening exercises performed by the patient himself being the best method in other cases.

2) The patient with chronic asthma will grow accustomed to that form of respiration which he uses in case of distress. He will mainly use the accessory muscles of respiration. The 'elevated chest' type of breathing is observed. Only a small portion of the lung volume is used in this form of respiration. What are the requirements to be met by respiration in patients with asthma?

As in the case of treatment to correct the posture, we should begin by asking ourselves the question, what we think we can obtain by altering the type of breathing to which the patient has grown accustomed.

(There also are people who claim that it is foolish to try to change the type of respiration in a patient, as the body itself will undoubtedly have found the best way out during attacks of dyspnoea).

Why then should we try to alter his elevated chest respiration? Should we attempt to direct his breathing into normal channels?

The larger the area involved, the larger the O_2 uptake, and therefore the less severe the dyspnoea will be. Moreover, as the air circulates more freely through the various air passages, ventilation, effectively removing particles of mucus, etc., will improve, which reduces the risk of infection, etc.

The era of technical science has resulted in the use of electric procedures The muscles are stimulated by an electric apparatus, which compels a type of artificially induced correct respiration, which becomes a habit.

The various types of breathing exercises can be discussed at great length or very briefly; one may choose between thoracic respiration, flank respiration, costo-abdominal respiration, pure abdominal respiration (and a variety of intermediate forms).

I do not wish to include the manner of working of the diaphragma, abdominal muscles and thoracic muscles and what type of synergy results in a particular form of respiration within the scope of this discussion.

One of the most valuable exercises consists in practising prolonged expiration The patient is given a watch (with a seconds-hand) or a stop-watch, is ordered to inspire deeply and then to expire deeply and as slowly as possible.

This exercise offers the advantage, that the patient is able to verify the result obtained and is able to see what improvement he has made.

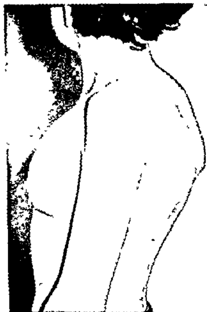


Fig 3



Fig 4



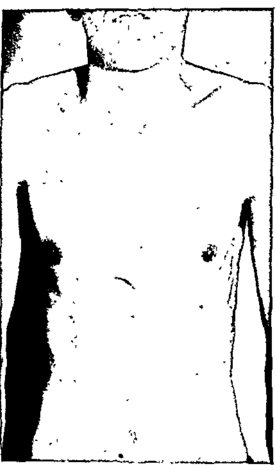


Fig 6



Fig 7



Fig 8



Fig 9

Fig 10

Fig 11

This method also serves to clear the chest completely. Accordingly the exercises initially frequently result in fits of coughing accompanied by the expectoration of viscid sputum. Another exercise, the results of which can be readily verified by the patient, is that in which a tape measure is employed (a leather band or belt may also be used) In our department of physical therapy we proceed on the assumption that the average patient must be able to achieve a difference of at least 10 cm between in- and expiration. The tape measure is applied around the lower part of the thorax. This method often results in a marked improvement in respiration. It obviously promotes flank respiration, during which the abdominal muscles remain tense.

In our opinion pure abdominal respiration, during which the abdomen projects like a balloon, to be subsequently drawn in again, has the considerable drawback, that ventilation (and therefore the removal of sputum) is not sufficiently stimulated, as this types of breathing chiefly affects the caudal portions of the lung.

Although I have been aided by an assistant, trained in César's method of kinesitherapy (fig. 10—11) in my own practice, both in the hospital and in the out-patients' department, for about 8 years, I continue to be convinced that he or she who tries to help the patient devotedly with all the power at his command, will obtain results, whether he belongs to an orthodox school, uses César's method, Mensendieck's system, Yogi therapy or any other method of treatment. The primary question is in what respect the breathing technique of the patient is deficient and by what method it can be improved.

So far our knowledges has not advanced sufficiently to enable us to definitely prefer one system to another. What is important, however, is the enthusiasm and perseverance of the instructor and the patient's persistence in performing the exercises himself Nothing will be achieved by 5 minutes or even 30 minutes a day. The patient must understand what the instructor wishes to accomplish and be shown the road to this goal.

The personal system used in the treatment of our patients is:

a) the hospitalized patient must frequently see to female instructress; the more he practises, the better (the risk of *too much exercising* need not be considered);

b) after examination all the out-patients are given instructions, to which other instructions are added in course of time. Now and then the results are checked and discussed with the patients;

c) in the case of children and patients with chronic asthma exercises are performed once or twice weekly, if possible for several years

In this connection I wish to take a stand against two views: the first being that treatment of children with so-called medical

gymnastics is a matter of months. Asthma therapy is a treatment of chronic patients, which is bound to involve a considerable period of time. This is also true of medical gymnastics. In these days, when allotments often have to be granted through the intermediary of medical officers employed by insurance companies, it is advisable to fully realize that the medical gymnastics instructor need not even begin treatment when the patient and medical officer are not both inclined to persevere.

Secondly, that physical therapy is useful only in children. From the preventive and curative point of view physical therapy is of importance in every case of chronic or frequently recurring asthma and striking results can even be obtained in a large number of chronic patients with a prolonged history of asthma. When we have exercised extensively with a patient with emphysema and a striking result has been obtained, both in his opinion and ours, another pulmonary function test shows *the reserve to be the case; only a subjective improvement has been* obtained; nevertheless, the performance of the patient will have in*creased considerably*

3) Exercises combined with movements.

A patient with chronic asthma was hospitalized for persistent dyspnoea in the daytime as well as at night. On hospitalization he was given medical treatment, which reduced the dyspnoea until treatment could be discontinued.

Among other things, we started performing breathing exercises. To my remark: 'so you see, that you can be free of symptoms', he replied: 'just wait until I am allowed up'. He was allowed up: 'just you see and wait until I'm allowed in the corridor'. He was allowed in the corridor, 'just wait and see until I'm allowed out of doors'. He went into the garden, 'just wait and see until I go about in the streets'. This game was constantly repeated until he was able to take 3-hour' walks. In the beginning he was accompanied by the instructor. During his movements his attention was continually directed toward breathing errors. Mentally he was helped to overcome his anxiety. Somatically, he was helped by obtaining a much better breathing technique. In studying the history of a large number of patients with asthma we are struck by the fact how often the patient states that his attacks of dyspnoea alternate with intervals marked by the absence of coughing and wheezing, except for laboured breathing, shortness of breath, a sense of constriction and even a slight dyspnoea after exercise.

The child stops playing or romping sooner than others, the adult is careful in running, going up and down the stairs, etc. The patient is just in balance in the resting state, but exercise results in dyspnoea (oxygen deficiency). As yet no emphysema has developed, however. A well-known story, which you can often hear tell, is that of the patient with

asthma who is just able to catch a train, starts running, has severe dyspnoea, continues running and, in a manner of speaking, runs through his dyspnoea.

A similar story may be told by certain patients with vasomotor rhinitis, whose nasal symptoms disappear on effort.

I have mentioned the case of the patient with emphysema, who showed a marked subjective improvement and a much better performance after vigorous breathing exercises, but failed to show any objective improvement. He has at least learnt to make a better use of the respiratory volume allowed him.

The asthmatic patient with chronic bronchitis and slight bronchiectases, who expectorates large quantities of mucus, will be grateful for the vigorous breathing exercises. He still has to eject his mucus, but he is at last relieved of his distressing cough reflexes and some viscid mucus. Expectoration, and therefore motion, is considerably facilitated. Although we personally are convinced that flank breathing is the ideal type of respiration in cases of asthma and can be kept up during movements, I am quite open to other opinions

The chief feature is the patience observed in exercising the patient. Actually I regard this as a form of training, there are many systems for running, rowing, swimming, etc ; some day one system may perhaps prove to be greatly preferable to all others, but so far one can only say that excellent results may be obtained by all systems, provided one perseveres in one's efforts. As a rule the increased performance is not due to the system of training, but to its persistent and vigorous use.

Our respiratory volume is completely sufficient when you or I have to walk slowly for 100 metres; it is also sufficient to climb the first stairs in houses on the Amsterdam 'grachten', but which of us arrives easily at the finish when we have to run 100 metres or climb the fourth staircase? Thanks to their training and increased performance, i.e. a better use of the body and respiratory volume, the runner and the Amsterdam doctor and milkman do indeed succeed in doing so.

The same applies to our patients with chronic asthma, who are in balance when walking slowly, but lose their balance when running. They also have to be trained. They must learn again to increase the respiratory volume granted to them, if possible, and at any rate to use it well and to perform the best possible movements. In treating these patients, the physician will keep asking himself how he can again increase the respiratory volume.

It is by no means sufficient to teach the patient to breathe correctly in bed or in his chair.

He must also be able to do something with his improved breathing technique.

For the time being those patients who also are often short of breath indoors will be grateful for this result. Patients, whose only symptom during the intervals consists in dyspnoea after exercise, will undoubtedly be more exacting in their demands, however.

4) Finally, there is an entirely different form of exercise: relaxation therapy. Uttering these words immediately calls to my mind certain patients, in whom everything seems to be spasmodic. They are often liable to dyspnoea, but their entire appearance gives the same impression. It are these cases in which the first thing to do is to consult a psychiatrist. But even then, there still remains that state of dyspnoea, of convulsiveness in their asthma and throughout their body

We first start giving these patients relaxation therapy (beginning with the phrase 'speak to your muscles', the patient, lying at his ease, being taught to consciously relax the muscles in every part of his body) I got acquainted with this form of therapy in the Physiotherapeutic Department of the Brompton Hospital (London). It undoubtedly affords relief to a number of patients.

Having been quietly taught how to relax their muscles, the tendency of the bronchial muscles to spasms will also decrease, I imagine; the dyspnoea diminishes, the sense of constriction disappears. This result is indeed sometimes obtained by the doctor visiting the patient in bed, by a quiet talk with the nurse, which takes the patient's mind off his condition, and even by going to the hospital; when this general spasmodic state disappears, the despair will also decrease spontaneously.

Undoubtedly not every attack of asthma can be controlled by relaxation of the muscles and nervous as well as mental relaxation. Acute severe dyspnoea fails to respond to words spoken to the patient.

The patient cannot and does not wish to lie down in a relaxed state; in that case a physiologic saline solution, administered as if it were the best possible drug, will certainly be of no avail; the patient looks at you expectantly and finds that his dyspnoea fails to decrease.

It are these cases, marked by constant dyspnoea, agitation and wheezing, that show a favourable response to relaxation therapy.

Also, it usually are these cases which are cited to illustrate the fact that breathing exercises and relaxation therapy are a form of psychotherapy.

We must picture the various forms of dyspnoea to ourselves:

acute severe dyspnoea, true status asthmaticus cannot be prevented or treated with breathing exercises or relaxation therapy. Here we are concerned with that form of dyspnoea, in which the patient develops severe symptoms, feels as if his breath were cut off and has a sense of constriction, the forms of chronic dyspnoea marked by unproductive cough and a wheezing breath, and especially those forms of chronic dyspnoea of a marked general spasmodic character, which do respond to treatment.

In addition, we are concerned with *prevention*: prevention of the sequelae of the chronic disease. The warning, uttered by Unger in his book, is also applicable in this case· Both statistical reports published by physiotherapeutists and reports on clinical cases are often characterized by the proud statement that excellent results have been obtained even when no additional antiallergic treatment was given

But it is impossible to report statistical data showing that treatment was completely successful in all cases.

Why not co-operate? Why should physical therapy not be regarded as a highly valuable adjunct? Does not a fractured bone first have to be set and heal completely, before the physiotherapeutist is able to restore movements involving the use of this bone? Attacks of asthma really are not due to a poor breathing technique; many individuals have an equally poor breathing technique, but nevertheless they do not wheeze

The same is true of asthma. Certain conditions associated with asthma are treated, certain sequelae of asthma are prevented, but there is no successful treatment of asthma and even the next genuine attack is not prevented.

Finally, I wish to add some words concerning other possibilities in the same field. The cheapest and yet a very good form of breathing exercise and correction of posture is swimming. Moreover, the psychologist will be able to tell you how important it is to experience the sensation of the light body floating in the water. A similar sensation is experienced in ballet-dancing, when the feeling of gliding over the dance-floor induces a beautiful and valuable sense of body control Breathing exercises are essential to good singing But on the other hand, are not the drawn-out tones in singing excellent expiration exercises? Especially in young children these forms of singing, dancing and exercise during the performance of fairy-tales often are effective in attaining the end desired.

SUMMARY

The purpose of physical therapy is:

a) the prevention or correction of changes in posture and deformities;

b) improvement of the type of breathing,

c) to increase the power of endurance, while retaining the correct breathing technique during movements;

d) relaxation therapy.

Various forms of chronic asthma respond very favourably to this treatment.

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DISCUSSION

K. H. BAAGÖE

Just a few words about abdominal breathing in the treatment of asthmatic patients.

First I want to mention that I know and have used, though only for a short time, two systems of exercises, the British 'Physical Exercises for Asthma', published by Asthma Research Council (1935), and the Danish system originated by Hans Heckscher (1946).

However, when I have not used these two systems to any greater extent it is chiefly because nearly all my patients are dealt with in a consulting practice and come from far away and must be finished with in one consultation.

So in recent years I have confined myself to teaching my patients two exercises which can be learned by most patients in a few minutes and the principal aim of which is to make the patients breathe abdominally, secondarily they are exercises in relaxation.

Besides, by confining the exercises to abdominal breathing I have thought that I should be able to get information about the importance that one can ascribe to this form of breathing, which forms part of the various respiratory systems.

The one is taken from Heckschers exercises. In this the patient with the flexed knees and hips bends forward with the head resting on the hands in a completely relaxed position If the patient now lies completely relaxed, abdominal breathing takes place spontaneously.

The second exercise is number one in the British system and consists in the patient lying back with knees drawn up and one hand placed on the belly to make sure that the breathing is done with the abdomen.

Nearly all patients can learn these excercises in a single consultation. I have only told them to breathe with the abdomen and not instructed them to breathe particularly deeply.

If the patients can perform these two exercises without difficulty at the first consultation, which shows that they have control of their respiratory muscles, [illegible]

I do not know how many of my patients continue these exercises after getting home. I can only state that the majority of the patients who have consulted me again have performed the excercises at home and have stated that the exercises helped them

The effect of the abdominal breathing is best illustrated by some examples.

1) A young girl of 23 had for 5 years been suffering periodically from mild asthmatic attacks. When she first consulted me, I found ronchi over both lungs [illegible]

a cold she said At the examination no ronchi were heard, and when I told her this, she exclaimed· ,Oh' I can easily manage to wheeze', and while she had hitherto breathed abdominally, as I had taught her, she now took a few deep breaths with the thorax with the result, that ronchi were heard over both lungs [illegible] she could abort the attack in this way.

Some time after, I got a letter from her, in which she told me that she had made the attempt, but had failed. For if she tried to breathe so little with the chest that the wheezing stopped, she could not get sufficient air so that she soon had to start breathing abdominally—with the usual good result.

2) A 31 year old working man with asthma, told me that if he took a few abdominal breaths now and then, he could take his midday rest lying on his back, which he had not been able to do before. He also did these exercises at night after he had gone to bed, as he felt that he got more air into the lungs in this way and consequently slept better

3) Another patient, a labourer of 62, who besides asthma had clinical emphysema, was very unwilling and sulky, when I showed him these exercises So I was greatly surprised when during a consultation 6 months later he told me, that he did the exercises every evening, and the most remarkable thing was that he stated that he could make wheezing, caused by cycling against the wind, stop by breathing abdominally while still cycling, in the same way he could stop wheezing when he carried heavy weights.

All together the statements of the patients agree. They say that they have the feeling that they 'get more air into the lungs' by abdominal breathing and that they can stop mild attacks, and a few say that they expectorate more easily.

However, I have not found any lasting improvement of the asthma It is only a symptomatic remedy, but one which the patient has at hand and which is useful whether he has emphysema or not. I consider it an important supplement in the treatment of asthma in a consulting practise.

Concerning the cause of the good effect one might think it was a psychic one, owing to the patients attention being diverted from the attack. This hypothesis is not supported by the case mentioned above, in which the patient could make wheezing come and go at will Further, one might think that the breathing was less deep in abdominal respiration, but this does not seem to be the case in the patient mentioned above; nor has a spirometric examination shown any difference in ventilation during abdominal and thoracic respiration in these patients.

According to Wyss's demonstration of the importance of the diaphragmatic spasm in the asthmatic attack, it seems to be most probable, that it is the conscious abdominal respiration that can overcome a mild diaphragmatic spasm

LE TRAITEMENT DE L'ASTHME PAR LA CORTICOTHÉRAPIE D'APRÈS 95 OBSERVATIONS

par

PASTEUR VALLERY-RADOT, CL. LAROCHE ET GILLES LYON

Nous rapporterons ici les résultats obtenus chez 95 malades atteints d'asthme sévère, que nous avons traités depuis 1950.

Tous ces malades ont été suivis pendant plus de trois mois et 65 ont été suivis pendant un à cinq ans. Lorsque le traitement fut entrepris, il existait un état de mal asthmatique: dyspnée permanente depuis plusieurs jours ou plusieurs semaines, sur laquelle se greffaient des accès paroxystiques. Certains malades étaient cyanosés et présentaient une tachycardie et même, dans 5 cas, des signes d'insuffisance ventriculaire droite.

Voici comment se décompose la statistique de nos 95 malades:

1°. 58 malades ont reçu un seul traitement hormonal: A.C.T.H. dans 36 cas, cortisone dans 21 cas, hydrocortisone dans 1 cas;

2°. 21 malades, à la suite de rechutes, ont dû subir plusieurs cures successives.

10 d'entre eux ont eu deux cures successives:
- deux cures d'A C.T.H. dans 4 cas,
- une cure d'A.C.T.H. puis une cure de cortisone dans 5 cas,
- une cure d'A C.T.H. puis une cure d'hydrocortisone dans 1 cas.

8 ont eu trois cures successives:
- trois cures d'A.C.T.H. dans 4 cas,
- deux cures d'A.C.T.H. et une cure de cortisone dans 3 cas,
- deux cures d'A C.T.H. et une cure d'hydrocortisone dans 1 cas.

2 ont eu quatre cures successives d'A C.T.H. dans 1 cas, de cortisone dans l'autre.

1 a reçu en quatre ans 22 cures successives, soit une cure environ tous les deux mois. L'A.C.T.H. et la cortisone ont été alternées.

Ainsi, nous avons pratiqué chez ces 21 malades: 48 cures d'A.C.T.H. 24 cures de cortisone, 2 cures d'hydrocortisone.

3°. 16 malades ont reçu des traitements prolongés sans interruption pendant plus de trois mois; nous étudierons plus loin les problèmes que pose cette méthode.

Si l'on excepte les traitements prolongés, chaque cure d'A.C.T.H.

ou de cortisone a duré en moyenne dix à quinze jours; elle a été plus longue lorsque, après ce laps de temps, l'auscultation révélait la persistance de sibilances dans les champs pulmonaires ou lorsque le sujet présentait encore de légères crises ou une dyspnée à l'effort. Nous avons été ainsi amenés, dans certains cas, à poursuivre le traitement hormonal pendant vingt à trente jours, en abaissant progressivement les doses.

Posologie

L'A.C.T.H. était injectée par *voie intramusculaire*, à raison d'une injection toutes les six heures pour les doses d'attaque. Au-dessous de 100 mgr. par jour, nous espacions les injections toutes les huit ou douze heures.

Le fractionnement des doses est indispensable, étant donné la courte durée d'action du produit

Nous avons fait parfois des *perfusions* d'A.C.T.H. par voie veineuse en injectant lentement, en six à huit heures, de très faibles quantités d'A.C.T.H (10 à 20 mgr. par jour), dissout dans 500 cc. de sérum glucosé. Ces perfusions ont l'inconvénient de nécessiter une surveillance très étroite du malade et, en particulier, de sa pression artérielle pendant toute la durée de l'injection; cependant, chez nos malades, nous n'avons jamais observé d'élévation tensionnelle notable.

Si, avec la perfusion, la sédation de la dyspnée a été parfois très rapide, s'effectuant dès la quatrième heure, l'efficacité de cette méthode ne nous a pas paru supérieure à celle des injections intramusculaires.

Nous avons injecté dans quelques cas l'A.C.T.H. par la *voie intradermique*, mais les résultats ont été très inconstants. Très bien supportées chez certains malades, les injections intradermiques ont provoqué chez d'autres des réactions locales douloureuses et l'hormone n'a pas eu ses effets habituels, du fait de la mauvaise résorption du produit.

Nous avons récemment employé, dans 2 cas, une solution d'A.C.T H.-*retard* cette solution est à recommander dans les traitements de longue durée car elle permet de limiter les injections et de diminuer la dose de l'hormone. Cependant, dans les états de mal où l'on veut obtenir une action rapide, il est préférable d'utiliser les solutions ordinaires.

La *cortisone* a été administrée, chez nos premiers malades, par la voie intramusculaire; nous avons ensuite utilisé exclusivement la voie gastrique qui nous a donné des résultats aussi satisfaisants. Elle ne fait pas courir le risque d'une infection aux points d'injection. La rapidité d'action, quand on utilise la voie gastrique, serait même augmentée si l'on en juge par la chute des éosinophiles du sang et par la disparition des symptômes cliniques.

Pour le traitement d'attaque, la dose quotidienne de cortisone était

divisée en quatre à six prises, réparties également dans les 24 heures. Les prises étaient espacées quand, à la fin du traitement, les doses étaient diminuées.

Le fractionnement des doses est encore plus important pour *l'hydrocortisone* que pour la cortisone car la durée d'action de l'hydrocortisone de dépasse guère six heures

Quelle que soit l'hormone utilisée, les doses doivent toujours être fortes d'emblée, puis progressivement dégressives

Pour l'A C.T.H., les doses d'attaque ont varié entre 100 et 150 mgr. par jour, en quatre injections. Ces doses étaient continuées pendant trois à huit jours, puis abaissées graduellement.

Il ne faut pas abaisser les doses d.A.C.T H. trop vite: il faut s'efforcer d'obtenir une disparition totale, non seulement de la dyspnée et de la toux, mais des sibilances pulmonaires, sinon la rechute est toujours rapide. Cette action complète de l'hormone ne s'observe guère avant le huitième jour; on ne doit donc pas donner une dose inférieure à 75 mgr avant le huitième ou le dixième jour. On peut terminer la cure par de faibles doses (50 puis 25 mgr.) destinées plus à éviter un sevrage hormonal brutal et une insuffisance surrénale secondaire qu'à agir directement sur l'état asthmatique. La cure dure donc en moyenne dix à quinze jours, avec un total de 700 à 1.500 mgr. d'A.C.T.H., ce chiffre étant très variable selon les sujets.

Il n'y a aucun rapport entre la dose totale d'A.C T H. et la rémission. Il est donc inutile de prolonger la cure

Si, après les quarante-huit premières heures de traitement, on n'a pas obtenu d'amélioration, on peut élever les doses, à 200 mgr. par our par exemple; il n'est pas rare d'observer ainsi une action favorable; en effet, il semble exister, pour chaque patient, une dose-seuil au-dessous de laquelle l'A.C.T H est inactive.

Si l'état de mal persiste après trois ou quatre jours malgré des doses élevées d'A.C.T.H., il faut essayer une autre hormone, de préférence l'hydrocortisone.

Les traitements avec la *cortisone* et avec *l'hydrocortisone* sont régis par les mêmes règles que celles que nous venons d'énoncer pour l'A C.T.H

La dose initiale doit être assez élevée, entre 150 et 200 mgr. par jour pour la cortisone, 100 à 125 mgr. pour l'hydrocortisone. Ces doses sont poursuivies pendant trois à huit jours, puis abaissées progressivement afin d'éviter les accidents de sevrage hormonal

La dose totale de cortisone est d'ordinaire un peu plus élevéeq ue pour l'A.C.T.H et se situe entre 1.000 et 2.000 mgr. administrés en dix à quinze jours.

Les doses d'hydrocortisone sont d'habitude de 30 p. 100 inférieures à celles de la cortisone

Faut-il faire suivre les cures d'A.C.T.H. par quelques prises de cortisone ou d'hydrocortisone et, réciproquement, les cures de cortisone ou d'hydrocortisone par quelques injections d'A.C.T.H.? Cette technique a été proposée par certains auteurs pour prévenir une insuffisance surrénale. Elle ne nous a pas paru particulièrement utile. Il ne semble pas que l'on puisse redouter un épuisement des surrénales par l'A.C.T.H. ou une insuffisance surrénale transitoire après la cure de cortisone.

Résultats

Les résultats obtenus avec l'A.C.T.H., la cortisone ou l'hydrocortisone varient beaucoup suivant que l'on considère les résultats immédiats ou la durée de rémission de l'asthme après la fin de la cure.

Ces trois hormones nous ont permis d'obtenir une sédation plus ou moins rapide des symptômes fonctionnels chez 80 malades. Nous avons eu 15 échecs, parmi lesquels certains malades ont ressenti une légère amélioration de la dyspnée, mais avec persistance d'un essoufflement permanent et de paroxysmes encore pénibles, en particulier nocturnes. Parmi ces 15 échecs, il y eut 4 morts, dans le classique tableau d'asphyxie, et l'autopsie a révélé les lésions habituelles de l'état de mal asthmatique, caractérisées par un encombrement très marqué des bronches.

Dans les cas favorables, l'action du traitement s'est manifestée d'ordinaire dans les vingt-quatre premières heures par une atténuation progressive de la dyspnée et de la cyanose et par la diminution de violence des accès paroxystiques; les malades ressentaient un soulagement remarquable et retrouvaient le sommeil. Il persistait encore pendant deux à trois jours des petites crises dyspnéiques ainsi qu'une recrudescence de l'essoufflement au moindre effort. L'expectoration diminuait souvent et même pouvait disparaître complètement: cet assèchement s'explique par la disparition de l'oedème de la muqueuse bronchique sous l'effet des hormones; la bronchoscopie montre un affaissement de la muqueuse qui reprend une coloration normale. Cependant, dans certains cas, la bronchorrhée pouvait être encore assez abondante pendant quelques jours, mais prenait un aspect muqueux et fluide. Les cellules éosinophiles disparaissaient de l'expectoration très souvent dès le deuxième jour du traitement.

Les sibilances pulmonaires persistaient encore quelques jours après la sédation de la dyspnée.

L'action immédiate de la corticothérapie sur l'état de mal asthmatique est donc souvent très remarquable. *Les résultats à distance* sont beaucoup moins brillants. Voici les résultats.

Dix asthmatiques ont bénéficié de la corticothérapie pendant un laps de temps supérieur à six mois: des crises assez sévères ont réapparu chez l'un d'eux au bout de six mois, chez 2 autres au bout d'un an, chez 2 autres au bout de deux ans; 5 autres n'avaient pas encore eu de rechutes de l'état de mal après six mois (1 cas), après deux ans (1 cas), après quatre ans (2 cas), après cinq ans (1 cas).

Chez 5 malades, la durée de la rémission n'a pas dépassé trois à six mois.

Chez 14 autres, la rémission ne fut que de un à trois mois.

Tous ces sujets avaient été libérés complètement de leur asthme à la fin du traitement. Certains conservaient une légère dyspnée d'effort ou voyaient réapparaître quelques crises dyspnéiques facilement combattues par les thérapeutiques habituelles, mais ils avaient repris une vie normale.

Dans 26 cas, la rechute s'est produite moins d'un mois après l'arrêt du traitement et, dans 18 cas, dès l'arrêt de celui-ci.

Dans 7 cas nous n'avons pu savoir la durée de la rémission.

Peut-on prévoir l'effet du traitement? Il semble que non. Que l'asthme soit allergique ou dû à une surinfection bronchique, qu'il soit sévère ou non, qu'il soit récent ou ancien, que le sujet soit jeune ou âgé, les résultats sont imprévisibles.

La reprise de l'état de mal nous a amenés à pratiquer *plusieurs traitements hormonaux successifs* (dont nous avons donné plus haut le détail).

Ces cures successives nous ont permis de *comparer* chez les mêmes malades *l'efficacité* de l'A.C.T.H., de la cortisone et de l'hydrocortisone.

Nous n'avons pas noté de différence sensible entre les effets de l'A.C.T.H. et ceux de la cortisone: ces deux hormones donnent d'ordinaire des résultats identiques lorsqu'elles sont utilisées chez le même malade. La cortisone administrée par voie buccale et à doses assez élevées (plus de 100 mgr. par jour) a une action aussi rapide que l'A.C.T.H. et la qualité de l'amélioration immédiate de même que la durée de la rémission ne varient guère avec le produit employé. Néanmoins, certains sujets réagissent mieux à l'une des hormones qu'à l'autre.

On pouvait penser que la mesure de la réponse surrénalienne à l'incitation corticotrope par le test de Thorn permettrait de prévoir le degré d'efficacité de l'A.C.T.H. Comme nous l'avons écrit dans un article précédent, [1] nous n'avons pu observer aucun parallélisme entre

[1] PASTEUR VALLERY-RADOT, LAROCHE, CL., MILLIEZ, P. DOMART, A. et RENIER, J.-C. L'A.C.T.H. et la cortisone dans le traitement de l'état de mal asthmatique. *Bull. et Mém. Soc. méd. des Hôp.*, Paris, 68, 319, 1952

la chute de l'éosinophilie et l'action thérapeutique. Des malades présentant des tests négatifs ont été très améliorés par l'A.C.T.H., tandis que des échecs coïncidaient avec des tests positifs. On sait d'ailleurs que la valeur du test de Thorn est très relative chez les sujets présentant une éosinophilie sanguine élevée

Nous n'avons, de l'hydrocortisone, qu'une expérience trop récente pour établir une comparaison valable avec les deux autres hormones. Néanmoins, nos premières constatations ont été très satisfaisantes puisque, sur 10 cures d'hydrocortisone, nous n'avons pas observé d'échec. Bien plus, nous avons eu de bons résultats chez 5 malades qui n'avaient pas été améliorés par l'A.C.T.H. ou la cortisone. Il semble donc que l'hydrocortisone possède une efficacité au moins égale et peut-être supérieure à celle des deux hormones précédentes.

Un certain nombre d'auteurs pensent que, chez les sujets soumis à des cures multiples d'A.C.T.H ou de cortisone, ces hormones perdent une partie de leur efficacité. Nos constatations ont été différentes: des cures hormonales successives nous ont donné des résultats assez concordants.

Malgré le danger de la *corticothérapie prolongée*, nous avons été amenés à faire chez 16 sujets des traitements continus. [1] Il s'agit d'asthmatiques dont la dyspnée avait cédé sous l'effet du traitement hormonal, mais réapparaissait dès la fin du traitement.

Nos premiers malades ont reçu de l'A.C.T.H., mais nous utilisons actuellement plus volontiers la cortisone ou l'hydrocortisone dont le mode d'administration par voie buccale est plus simple.

La *durée des cures* a été variable, de deux mois à trois ans

Quatre malades ont été traités pendant plus d'un an avec d'excellents résultats. L'un d'eux fait depuis trois ans des cures alternées de cortisone et d'A.C.T.H. à des doses variant entre 50 et 100 mgr. par jour. Un deuxième a obtenu, par la même méthode, un soulagement complet pendant deux ans, puis a été perdu de vue; nous avons appris qu'il était mort récemment d'un accident vasculaire, indépendant de son asthme. Un troisième prend, sans interruption, 75 mgr. de cortisone depuis un an Le quatrième, soumis d'abord à une cure continue de cortisone (75 mgr. par jour) pendant trois ans, prend actuellement depuis trois mois 10 mgr. d'hydrocortisone six jours par semaine.

Huit autres malades ont été traités pendant deux à trois mois avec des rémissions totales par l'hydrocortisone (3 cas), l'A.C.T.H. (1 cas), des cures successives de cortisone et d'hydrocortisone (1 cas), d'A.C.T.H

[1] Certains ont été suivis par le Dr. B. HALPERN.

et de cortisone (2 cas) ou des trois hormones (1 cas). La corticothérapie a pu être arrêtée chez 2 d'entre eux, après deux mois, sans qu'il apparût de rechute. Les 6 autres restent soumis au traitement hormonal qui ne peut être interrompu sans une reprise immédiate de la dyspnée.

Sur 16 malades nous n'avons eu que 3 échecs et 1 résultat médiocre. Les 12 autres malades conservent, la plupart, un léger essoufflement à l'effort et quelques râles sibilants, mais ils mènent une vie normale; ils ne souffrent plus de dyspnée permanente ni d'accès asthmatiques paroxystiques.

La dose-seuil, au-dessous de laquelle réapparaissent des symptômes fonctionnels gênants, est située suivant les sujets entre 50 et 100 mgr. d'A.C.T.H. ou de cortisone par jour. Elle varie d'ailleurs, chez un même sujet, et peut s'élever sous l'influence de certains facteurs, tels qu'une infection respiratoire. Les malades règlent eux-mêmes leur traitement, au bout de quelques mois, en utilisant la dose minimum active.

Dans certains cas, l'action de la cortisone semble s'épuiser, mais des injections d'A.C.T.H. pendant quelques jours semblent rendre le sujet de nouveau sensible à l'hormone surrénale.

Turiaf[1] pense qu'il est préférable de n'administrer la cortisone et l'hydrocortisone que cinq jours par semaine, mais l'interruption de deux jours est parfois suffisante pour amener une reprise de la dyspnée.

Bickernan et Barach[2] ont essayé de donner une dose forte de cortisone (400 mgr) un jour par semaine, mais les résultats ont été très décevants

La dose efficace d'hydrocortisone est plus faible que celle de cortisone. Turiaf la situe entre 30 et 40 mgr. par jour.

Nous avons employé récemment l'A.C.T.H.-retard avec succès chez 2 malades: l'un reçoit chaque jour une injection de 40 mgr. de cette solution, la dose d'A.C.T.H. a été ainsi réduite chez lui des deux tiers Chez l'autre malade, 40 mgr. d'A.C.T.H.-retard donnent le même résultat que 75 à 100 mgr. d'A.C.T.H. ordinaire et seraient plus efficaces que 100 mgr. de cortisone ou 80 mgr. d'hydrocortisone.

Nous pensons qu'il est utile d'intercaler, pendant les cures prolongées de cortisone ou d'hydrocortisone, quelques injections d'A.C.T.H., toutes les quatre à six semaines, afin de stimuler les cortico-surrénales et d'éviter leur aplasie.

[1] TURIAF, J., MASLAND, P. et JEANJEAN, Y. Le traitement au long cours des asthmes à dyspnée continue par l'hydrocortisone en comprimés *Revue des Praticiens, 4,* 1954 3037-3040

[2] BICKERMAN, H. et BARACH, A. Comparative results of the cure of ACTH, cortisone and hydrocortisone in the treatment of intractable bronchial asthma and pulmonary emphysema *(J. Allergy) 25,* 312-324, 1954

Précautions à prendre pour éviter accidents et incidents

L'A.C.T.H., la cortisone et l'hydrocortisone sont des corps dont l'utilisation n'est pas dépourvue de danger. Ils ne doivent être employés qu'à bon escient, dans des asthmes graves où les thérapeutiques usuelles ont échoué. Cette restriction, que nous avions formulée dès 1952, nous paraît conserver toute sa valeur

Nous avons systématiquement soumis nos asthmatiques pendant le traitement à un régime sans sel. Nous leur avons donné quotidiennement 1 à 2 gr. de chlorure de potassium et nous leur avons fait prendre un antibiotique (d'ordinaire tifomycine ou terramycine).

Nous n'avons jamais noté d'accidents oedémateux ou hypertensifs. Les augmentations de poids ont été faibles et n'ont guère dépassé 2 à 3 kilos; encore faut-il souligner que les grands asthmatiques sont souvent

L'hydrocortisone entraîne souvent, après quelques jours, une augmentation de la diurèse qui peut être passagère ou persister pendant toute la cure; aussi les malades soumis à cette hormone présentent-ils assez souvent une légère perte de poids. Il n'y a donc peut-être pas lieu de craindre ici la rétention sodique et ce serait un des avantages de l'hydrocortisone.

L'arrêt du traitement hormonal est parfois suivi d'hypotension modérée et d'asthénie; cette insuffisance surrénale passagère n'est jamais dangereuse si l'on a eu soin de ne pas suspendre brusquement la corticothérapie, mais d'abaisser progressivement les doses. Chez un de nos

stration de sérum glucosé et chloruré, de désoxycorticostérone et de 200 mgr. de cortisone a amené une sédation rapide.

Nous avons traité, sans accident, des asthmes infectés, mais nous avons soumis, dans ces cas, les malades à des doses plus élevées d'antibiotiques. Cette antibiothérapie préventive pose un problème délicat au cours des cures très prolongées: doit-elle être continuée sans arrêt pendant des mois et ne perd-elle pas, dans ces conditions, une partie de son efficacité? Nous avons vu, en effet, apparaître, au quatrième mois d'un traitement alterné par l'A.C.T.H. et la cortisone, une infection pulmonaire grave avec des foyers congestifs multiples et bilatéraux, bien que la tifomycine n'ait jamais été cessée. La guérison a été obtenue grâce à l'association d'autres antibiotiques (pénicilline et streptomycine).

Des troubles psychiques apparaissent parfois: insomnies, irritabilité. Nous avons observé, au cours d'une cure d'A.C.T.H., un syn-

drome dépressif particulièrement grave, qui a abouti au suicide.

Nous n'avons jamais noté, même au cours des cures prolongées, de symptômes sévères d'hypercorticisme: les sujets ont développé parfois une légère obésité, avec aspect arrondi de la face, de l'acné, mais n'ont jamais présenté ni glycosurie, ni hypertension artérielle ni ostéoporose.

Deux malades, peu améliorés par une cure d'A.C.T.H., sont morts dans un état de mal asthmatique, l'un vingt-sept, l'autre trente-quatre jours après la cure hormonale. Il est difficile de dire si l'A.C.T.H. a joué un rôle néfaste dans ces deux cas. Mais, après les traitements par corticothérapie, il nous semble prudent de soumettre les malades pendant plusieurs semaines à une surveillance médicale très rigoureuse et de recourir à un nouveau traitement par la cortisone en cas de rechute grave de l'état de mal asthmatique.

Les injections d'A.C.T.H. peuvent entraîner une sensibilisation à ce corps; nous l'avons observé dans un cas: au début d'une seconde cure, le malade a présenté de l'urticaire et une recrudescence violente de la dyspnée, alors qu'une première cure avait été bien supportée.

RÉSUMÉ

Les auteurs ont traité 95 asthmatiques en état de mal par A C.T.H. cortisone ou hydrocortisone Ces trois hormones, dont l'activité est très comparable, ont permis d'obtenir une sédation rapide des symptômes chez 80 malades. Parmi les 15 échecs, il y eut 4 morts; l'autopsie révéla les lésions habituelles de l'état de mal asthmatique.

Les résultats à distance ont été très variables: 10 asthmatiques seulement bénéficièrent de la corticothérapie pendant plus de six mois

Chez 16 malades fut pratiqué un traitement hormonal prolongé (deux mois à trois ans). Il n'y eut que 3 échecs et 1 résultat médiocre. La dose-seuil était située suivant les sujets entre 50 et 100 mgr. d'A.C.T H. ou de cortisone par jour.

N B. Depuis que ce rapport a été rédigé, nous utilisons surtout la delta-cortisone.

ACTH, CORTISONE AND HYDROCORTISONE IN THE TREATMENT OF ASTHMA

A study based on ninety-five cases

by

PASTEUR VALLERY-RADOT, CL. LAROCHE AND GILLES LYON

We shall here report the results obtained in 95 patients affected with severe asthma and treated since 1950.

All these patients were studied for over three months and 65 were studied for periods ranging from one to five years. When treatment was started, the patients were affected with status asthmaticus, marked by dyspnoea which had continued for several days or weeks and which was aggravated by paroxysmal attacks. Some patients were affected with cyanosis and tachycardia and, in 5 cases, even showed symptoms of right ventricular failure.

These are the statistical data on our 95 patients:

1) 58 patients were given a single treatment with hormones: ACTH in 36 cases, cortisone in 21 cases, hydrocortisone in 1 case;

2) 21 patients, who had relapses, were given several courses of treatment in succession.

Of these patients, 10 were given two courses of treatment in succession:
- two treatments with ACTH in 4 cases;
- one treatment with ACTH followed by one treatment with cortisone in 5 cases;
- one treatment with ACTH followed by one treatment with hydrocortisone in 1 case.

8 were given three courses of treatment in succession:
- three treatments with ACTH in 4 cases;
- two treatments with ACTH and one treatment with cortisone in 3 cases;
- two treatments with ACTH and one treatment with hydrocortisone in 1 case.

2 were given four treatments in succession, ACTH being administered in one case, cortisone in the other.

One patient was given 22 successive treatments in four years, i.e. approximately one treatment every two months. ACTH and cortisone were given alternately.

Accordingly, these 21 patients were given 48 treatments with ACTH, 24 treatments with cortisone and 2 treatments with hydrocortisone.

3) 16 patients were given prolonged treatments continued for over three months; later we shall study the problems raised by this method.

With the exception of the prolonged courses of treatment, each treatment with ACTH or cortisone was continued for an average period of ten to fifteen days; it was continued beyond this period when subsequent auscultation revealed the persistence of sibilant rales in the lungs or when the subject continued to have slight attacks or showed dyspnoea after exercise. Therefore we continued to give hormones for twenty to thirty days in certain cases, the doses being progressively reduced.

Dosage

ACTH was injected *intramuscularly*, one injection being made every six hours when the initial doses were given. When administering less than 100 mgm. daily, the injections were made at eight- or twelve-hour intervals.

Fractionation of the doses is essential, in view of the short action of the drug.

In some cases we administered ACTH by *intravenous drip*, very small doses of ACTH (10–20 mgm. daily), dissolved in 500 ml of glucose solution, being slowly injected in a period of from six to eight hours. The drawback to intravenous drip is that close supervision of the patient, and especially of his blood pressure, is essentail throughout the injection; we never observed any marked rise in blood pressure in our patients, however.

Although intravenous drip afforded very rapid relief of the dyspnoea in some cases, relief being obtained within four hours, we do not believe this method to be more effective than intramuscular injections.

In some cases we injected ACTH *intradermally*, but the results were very inconstant. Although extremely well tolerated by some patients, the intradermal injections gave rise to painful local reactions in others and the hormone failed to have its usual effects owing to deficient absorption of the drug.

We have recently used a solution of ACTH-'*retard*' in 2 cases; administration of this solution is advisable in prolonged treatment, as less injections are required and the dose of hormone may be reduced. When, however, rapid action is essential, as in status asthmaticus, ordinary solutions are to be preferred.

Cortisone was administered intramuscularly in our initial cases; subsequently, the hormone was administered only by mouth, the results obtained being equally satisfactory. The latter method does not involve the risk of infection at the sites of injection. The rapid action is even

increased by oral administration, judging by the decrease of the number of eosinophils in the blood and the disappearance of the clinical symptoms.

The daily quantity of cortisone given during the initial treatment was divided into four to six doses, taken at equal intervals over 24 hours. The doses were given at longer intervals when the dosage was reduced towards the end of treatment.

Fractionation of the doses is even more essential when administering *hydrocortisone* than when giving cortisone, as the action of hydrocortisone barely continues beyond six hours.

Whatever hormone may be employed, the initial doses should be large and then be progressively reduced.

The initial doses of ACTH varied from 100 to 150 mgm. daily, given in four injections. These doses were continued for three to eight days and then were gradually diminished.

The doses of ACTH should not be reduced too rapidly; an attempt should be made to obtain the complete disappearance, not only of the dyspnoea and cough, but also of the sibilant rales in the lung, otherwise there is bound to be a rapid relapse. This complete action of the hormone is hardly ever seen to occur before the eighth day of treatment; therefore, a dose smaller than 75 mgm. should not be given prior to the eighth or tenth day. Treatments is concluded with the administration of small doses (50 and then 25 mgm.), intended to avoid too sudden withdrawal of the hormone and to prevent secondary adrenal insufficiency, rather than to exert a direct effect on the asthma. Accordingly, the average duration of treatment is from ten to fifteen days, a total dose of 700—1.500 mgm of ACTH being administered; this total dose varies markedly with the subjects.

There is no relationship between the total dose of ACTH and the length of the remission. Therefore it is useless to prolong treatment.

When no improvement has been obtained after forty-eight hours of treatment, the dose may be increased, e g. to 200 mgm. daily, this will frequently have a favourable effect; apparently, there is a liminal dose for each patient, below which ACTH is ineffective.

When the status asthmaticus persists after three or four days despite administration of large doses of ACTH, another hormone, preferably hydrocortisone, should be tried.

Treatments with *cortisone* and *hydrocortisone* are governed by the same rules as those applying to treatment with ACTH

The initial dose should be fairly large, 150—200 mgm. of cortisone and 100—125 mgm. of hydrocortisone being administered. These dosages are

continued for three to eight days and subsequently reduced progressively, to avoid complications resulting from sudden withdrawal of the hormone.

As a rule, the total dose of cortisone is somewhat larger than that of ACTH, varying from 1.000 to 2.000 mgm., administered within ten to fifteen days.

The doses of hydrocortisone usually are 30 per cent smaller than those of hydrocortisone.

Should courses of treatment wit ACTH be followed by administration of a few doses of cortisone or hydrocortisone and, conversely, should treatments with cortisone or hydrocortisone be followed by a number of injections of ACTH? This method has been suggested by certain authors, with a view to preventing adrenal insufficiency In our opinion, it is not a particularly useful method. It is unlikely that administration of ACTH will result in an impairment of adrenal function or that treatment with cortisone will be followed by transient adrenal insufficiency.

Results

The results obtained in treatment with ACTH, cortisone or hydrocortisone vary markedly according as to whether the immediate results or the length of remission of the asthma after the completion of treatment are considered.

These three hormones afforded more or less rapid relief of the functional symptoms in 80 patients. We had 15 failures, including a number of patients whose dyspnoea showed a slight improvement, but who had persistent shortness of breath and continued to be subject to distressing paroxysms, especially at night. Of these 15 patients in whom treatment failed, 4 died, showing the classical symptoms of asphyxia and autopsy revealed the usual lesions of status asthmaticus, characterized by marked obstruction of the bronchi.

When treatment was effective, it usually resulted in progressive relief of the dyspnoea and cyanosis and a decrease in severity of the paroxysmal attacks within the first twenty-four hours, the patients experienced considerable relief and were able to sleep again. Slight attacks of dyspnoea persisted for 2—3 days and the slightest effort continued to cause a recrudescence of the shortness of breath. Expectoration frequently decreased and occasionally even disappeared completely; this drying up was attributable to the disappearance of the oedema of the bronchial mucosa resulting from the action of the hormones; bronchoscopy revealed subsidence of the mucosa, which again assumed a normal colour; in some cases, however, bronchorrhoea continued to be profuse during a number of days, but showed a mucous and fluid appearance. Very often the eosinophils had disappeared from the expectoration as early as the second day of treatment.

The sibilant rales in the lungs persisted for a number of days after relief of the dyspnoea.

Accordingly, treatment with these hormones frequently has a marked *immediate effect* on status asthmaticus The *late results* are much less excellent. These are the results obtained:

Ten patients with asthma benefited by treatment for a period of over six months: fairly severe attacks recurred after six months in one case, after one year in 2 others and after two years in 2 other cases; 5 other patients had not had any relapses of status asthmaticus after six months (1 case), two years (1 case), four years (2 cases) and five years (1 case) respectively.

Remission did not continue beyond 3–6 months in 5 cases. The symptoms disappeared for only 1–3 months in 14 others.

All these subjects had been completely free from asthma at the end of treatment A slight dyspnoea after exercise persisted in some cases or attacks of dyspnoea, readily controlled by the usual methods of treatment, recurred, but these patients had been able to resume a normal way of life.

Relapses occurred within less than a month after treatment had been discontinued in 26 cases and as soon as it had been discontinued in 18 cases.

We were unable to ascertain the length of the remission in 7 cases.

Can the result of treatment be anticipated? Apparently, the answer is: 'no'. Whether the asthma is of allergic origin or due to superinfection of the bronchi, whether it is severe or not, whether it is recent or long-standing, whether the patient is young or old, the results cannot be predicted.

The recurrence of status asthmaticus led us to give *several courses of hormonal treatment in succession* (which have previously been described in detail).

These successive treatments enabled us to *compare the effectiveness* of ACTH, cortisone and hydrocortisone in the same patients.

We did not observe any noticeable difference between the effects of ACTH and those of cortisone; the results obtained by administration of these two hormones usually are identical when they are used in the same patient. The action of large doses (over 100 mgm. daily) of cortisone administered orally is as rapid as that of ACTH and the degree of improvement as well as the length of the remission hardly vary with the drug employed Certain subjects, however, respond more readily to one hormone than to the other.

It might be thought that the degree to which the adrenals respond to

corticotrophic stimulation in Thorn's test would afford a standard by which to judge the effectiveness of treatment with ACTH. As we have stated in a previous paper,[1] we have not been able to observe any parallelism between the decrease in eosinophilia and the effect of treatment. Patients who had negative tests showed a marked improvement on treatment with ACTH, whereas failures coincided with positive tests. Thorn's test is, however, known to have merely a relative value in subjects showing marked eosinophilia.

Our experience of hydrocortisone has been too recent to enable any valid comparison with the two other hormones. Nevertheless, the first results obtained have been very satisfactory, as no failures were observed in 10 courses of treatment with hydrocortisone. And what is more, we obtained good results in 5 patients who had failed to show any improvement on treatment with ACTH or cortisone. Accordingly, the effectiveness of hydrocortisone apparently is at least equal to and possibly surpasses that of the other two hormones.

A certain number of authors believe that the effectiveness of the hormones will decrease in patients given several courses of treatment with ACTH or cortisone. Our findings have been different; the results which we obtained in successive treatments were markedly identical.

Despite the hazards attendant upon *prolonged treatment* with these hormones, we subjected 16 patients to continued treatment.[2] These were patients with asthma, whose dyspnoea had disappeared on hormonal therapy, but recurred as soon as treatment was discontinued.

Our first patients were given ACTH, but to-day we prefer using cortisone or hydrocortisone, oral administration of which is more simple.

The *duration of treatment* varied from two months to three years.

Four patients were treated for over a year and excellent results were obtained. Of these patients, one has been treated alternately with cortisone and ACTH for the last three years, the doses varying from 50 to 100 mgm. daily. This method afforded complete relief to another for a period of two years, after which he was not seen again; we learned that he had recently died from a vascular complication, occurring independently of his asthma. A third patient took 75 mgm. of cortisone without a break during the past year. The fourth patient, who initially underwent continued treatment with cortisone (75 mgm. daily) during

[1] PASTEUR VALLERY-RADOT, LAROCHE, CL., MILLIEZ, P., DOMART, A., RENIER, J.-C. L'A.C.T.H. et la cortisone dans le traitement de l'état de mal asthmatique. *Bull. et Mém. Soc. méd. des Hôp., Paris*, 68, 1952, 319.

[2] Some were studied by DR. B. HALPERN.

three years, has now been taking 10 mgm. of hydrocortisone six days a week for the last three months.

Eight other patients were successfully treated with hydrocortisone for 2–3 months (3 cases), ACTH (1 case), cortisone followed by administration of hydrocortisone (1 case), ACTH and cortisone (2 cases) or all three hormones (1 case). Treatment was discontinued within two months in 2 of these cases, without any relapse occurring. Treatment was continued in the 6 other cases, as discontinuation of treatment tended to result in immediate recurrence of the dyspnoea.

We had only 3 failures and 1 moderate result in 16 patients. A slight dyspnoea after exercise and some sibilant rales persisted in the greater part of the 12 others, who led a normal life, however; they were no longer affected with permanent dyspnoea or paroxysmal attacks of asthma.

The liminal dose, below which distressing functional symptoms recurred, varied from 50 to 100 mgm. of ACTH or cortisone daily with the individual subject. It also varied in a single subject, however, and tended to be increased by certain factors such as infection of the respiratory tract. Within a few months the patients were able to conduct their own treatment, using the minimum effective dose

Cortisone apparently became inactive in certain cases, but when injections of ACTH were given for a number of days, the subject again started to respond to treatment with cortisone

Turiaf[1] believes that it is advisable to administer cortisone and hydrocortisone for only five days a week, but in some cases a two-day interval will be sufficient to bring on a recurrence of the dyspnoea.

Bickerman and Barach[2] have tried giving a large dose of cortisone (400 mgm.) once a week, but the results were extremely disappointing.

The effective dose of hydrocortisone is smaller than that of cortisone. According to Turiaf it is from 30–40 mgm. daily.

Recently, we successfully used ACTH-'retard' in the treatment of 2 patients, one was given a daily injection of 40 mgm. of this solution, so that the dose of ACTH was reduced by two-thirds in this case. The result obtained in the other case with administration of 40 mgm. of ACTH-'retard' was identical to that of treatment with 75–100 mgm of ordinary ACTH, 40 mgm. of ACTH-'retard' being more effective than 100 mgr. of cortisone or 80 mgm. of hydrocortisone.

In our opinion, it would be useful to make a number of injections of

[1] TURIAF, J, MASLAND, P, JEANJEAN, Y. Le traitement au long cours des asthmes à dyspnée continue par l'hydrocortisone en comprimés *Revue des Praticiens*, *4*, 1954, 3037—3040.

[2] BICKERMAN, H, BARACH, A Comparative results of the cure of ACTH, cortisone and hydrocortisone in the treatment of intractable bronchial asthma and pulmonary emphysema. *J Allergy*, *25*, 1954, 312—324

ACTH every 4—6 weeks during prolonged treatments with cortisone or hydrocortisone, with a view to stimulating the adrenals and preventing atrophy of these glands.

Precautions to be taken to avoid complications and untoward reactions

ACTH, cortisone and hydrocortisone are substances, the use of which is not without danger. They should only be employed wittingly in cases of severe asthma, in which the usual methods of treatment have failed. *This restriction, which we have formulated as early as 1952, continues* to apply in our opinion.

We systematically placed our patients with asthma on a salt-free diet during treatment. We gave them 1—2 gr. of potassium chloride daily and we made them take an antibiotic (usually typhomycin or oxytetracycline).

We never observed complications consisting in oedema or hypertension. There were only slight gains in weight, hardly exceeding 2—3 kg.; in addition, the fact should be stressed that patients with severe asthma frequently show evidence of malnutrition and that a gain in weight *coincides with a recovery of appetite; therefore it cannot be attributed* only to retention of water and sodium in every case.

Within a few days, administration of hydrocortisone frequently results in increased urinary secretion, which may be transient or may persist throughout treatment; in addition, patients treated with this hormone often show a slight loss of weight. Therefore retention of sodium is an unlikely event in these cases, which is one of the advantages of treatment with hydrocortisone.

Discontinuation of treatment is occasionally followed by moderate hypotension and asthenia; this transient adrenal insufficiency is never dangerous, provided that the hormone is not suddenly withdrawn and the dosage is gradually reduced Sudden withdrawal of ACTH in view of an infection occurring in one of our patients resulted in acute adrenal insufficiency, associated with marked hypotension, tachycardia and disturbances of consciousness; administration of a glucose and chloride solution, desoxycorticosterone and 200 mgm. of cortisone afforded rapid relief.

We have successfully treated cases of asthma complicated by infection, but in these cases we administered larger doses of antibiotics to the patients. This preventive treatment with antibiotics confronts us with a difficult problem during very prolonged courses of treatment: should it be continued for months without a break and will not its effectiveness be reduced in these conditions? Thus a severe pulmonary infection, marked by multiple and bilateral congestive lesions, appeared in the fourth month of an alternating treatment with ACTH and cortisone,

although administration of typhomycin had been continued throughout this period. Combined treatment with other antibiotics (penicillin and streptomycin) resulted in the disappearance of the infection.

Mental disturbances such as insomnia or irritability appear in some cases. During a treatment with ACTH we observed a particularly severe depression, which resulted in suicide.

We have never observed severe symptoms of hyperfunction of the adrenal cortex, not even during prolonged courses of treatment; occasionally, the subjects developed a slight obesity, with a puffed face and acne, but they never showed glycosuria, hypertension or osteoporosis.

Two patients, who had shown little improvement on treatment with ACTH, died in a condition of status asthmaticus, one within twenty-seven, the other within thirty-four days after treatment had been discontinued. It is difficult to decide whether ACTH played a fatal part in these two cases In our opinion, however, treatment with these hormones should be followed by close medical supervision of the patients continued over several weeks and another treatment with cortisone is advisable if they should have a severe relapse of status asthmaticus.

Injections of ACTH may result in sensitization to this substance; this was seen to occur in one case, the patient showing urticaria and a severe recrudescence of his dyspnoea when a second course of treatment was started, whereas the first treatment had been well tolerated.

SUMMARY

The authors treated 95 patients with status asthmaticus with ACTH, cortisone or hydrocortisone. These three hormones, the effects of which bear a marked resemblance to one another, afforded rapid relief of the symptoms in 80 patients. Of the 15 patients in whom treatment failed, 4 died; autopsy revealed the usual lesions of status asthmaticus.

The late results varied markedly; only 10 patients treated with these hormones continued free from symptoms for a period of over six months.

Sixteen patients were given a prolonged treatment with hormones (from two months to three years) There were only 3 failures and 1 poor result. The liminal dose varied with the subjects, ranging from 50 to 100 mgm. of ACTH or cortisone daily.

N.B. Since this report was written, we specially use delta-cortisone.

LONG TERM TREATMENT OF ASTHMA WITH CORTISONE AND CORTICOTROPHIN

by

R. S. BRUCE PEARSON

Cortisone and A.C.T.H.A.R. gel are recognized to be of considerable value in the treatment of acute severe asthma. Their value as long term symptomatic remedies is less certain. In this paper the effect of treatment is recorded in twenty seven cases of intractable asthma with oral Cortisone (20) and intramuscular A.C.T.H A.R. gel (8). One patient received treatment with both substances Treatment was continued from three months to three years in 25 cases. In two, side effects led to termination of treatment with Cortisone within a few weeks. Cases were selected for the chronicity of their symptoms. Thirteen had been admitted to hospital in status on one or more occasions and the remaining eight were included because of their failure to respond to other measures. Eight patients had been unable to earn their living or do more than light housework for at least a year and eight lost long periods of time from work each year Three relatively mild cases were included

Results were judged on vital capacity readings which were in most cases recorded every two weeks on a fast moving drum, changes in attack rate and the quantity of spasmolytic drugs used and in the physical signs and capacity for work.

Dosage

Oral Cortisone was initially administered in doses varying from 300 to 100 mgm. daily and maintained at 35 – 100 mgm daily. Larger doses were not administered owing to the risk of causing side effects. A.C T.H A.R. gel was given in doses from 40 mgm. daily to 20 units weekly. Thirteen of the twenty seven patients were considered to have had excellent or good results (case 1 responded to both substances), one showed slight improvement and thirteen no response (See Table I).

If these cases are divided into those with persistent expiratory wheezing in addition to attacks of dyspnoea, and those with purely intermittent asthmatic symptoms, it is evident that the results are very poor in the former group. These patients were never at any time found to be

[1] I wish to express my thanks to Dr D V Bates for carrying out lung function tests in two cases. Fifteen of the patients treated with Cortisone were included in the Medical Research Council's *Controlled Trial of effects of Cortisone acetate in patients suffering from chronic asthma* (in publication) The conclusions reached in this paper are those of the author only

TABLE 1

Chronic or Recurrent Asthma (O Ps)

	No. of cases	Results				Deaths
Treated with Cortisone		Excellent	Good	Slight	None	
Persistent expiratory wheezing	10	0	1	1	8	0
Intermittent asthma	10	2	4	0	4	0
Treated with A.C.T.H.A.R. gel						
Persistent expiratory wheezing ...	5	0	4	0	1	0
Intermittent asthma	3	1	2	0	1	0
Total	28	3[1]	11	1	13	0

[1] One patient who responded excellently to Cortisone and A.C.T.H. is included in both groups

free from evidence of expiratory obstruction whenever they were examined before or during treatment. All had been under observation for at least one year and many for far longer.

Treatment with Cortisone

Of the twenty cases treated with Cortisone, ten had persistent wheezing and of these only two showed appreciable improvement, of the ten with intermittent attacks six did well.

Table 2 shows the results in ten of these cases who were each treated with Cortisone and Placebo tablets for alternate six month periods, separated by three months of symptomatic treatment. Eight cases were treated with the Placebo tablets for the first six month period and two with Cortisone. Five of this group had chronic persistent asthma and five intermittent attacks. *None of those with persistent asthma improved.* Two (1,8) of those with intermittent attacks showed unequivocal improvement as regards attack rate and increase in vital capacity, and on subjective and general clinical grounds. One other (4) did well on Cortisone but even better on Placebo and was therefore regarded as a failure as far as the effect of Cortisone treatment was concerned; another (10) claimed

TABLE 2

					Cortisone			Placebo		Symptomatic		
Case No	Sex	Age	Duration of asthma in years	Persistent Intermittent	Vital capacity	Attack rate for 2 week periods	Average daily dose in mgm.	Vital capacity	Attack rate for 2 week periods	Vital capacity	Attack rate for 2 week periods	Weight increase on Cortisone
1	M	36	2	I	2570	3	81	2160	49	1810	36	+ 24 lbs
2	F	40	14	P	1500	42	70	1390	32	1420	21	+ 6 lbs
3	F	44	34	P	1840	30	94	1760	10	1850	14	+ 1½ lbs
4	F	31	12	I	2200	3.8	82	2340	2	1920	10 5	+ 11 lbs
5	F	40	14	P	1640	49[1]	100	1850	78	1600	10 2	+ 16 lbs
6	F[2]	51	17	P	1500	constant	70	1550	constant	1350	constant	+ 8 lbs
7	M[3]	41	9	P	1700	constant	100	2100	constant	2250	constant	No change
8	F	31	20	I	2370	7	100	2100	16	2020	47	+ 10 lbs
9	F[4]	41	1	I	—	—	75	1900	48	2600	23	—
10	M	36	8	I	3070	3	100	3700	1	2860	0 5	+ 14 lbs

[1] Injections of Adrenalin (self-administered) were given 2—4 times daily during this period.
[2] Attack rate not recorded but nebuliser used 7—10 times daily over whole period Emphysema present
[3] Constantly wheezy throughout, taking 3—5 gr of Ephedrine and using inhaler 3—6 times daily Emphysema present
[4] Cortisone therapy terminated after 4 weeks because of depression

to be much improved on Cortisone but his attack rate did not reflect this, and the vital capacity showed a considerably better average on the Placebo than on Cortisone Thus improvement in two cases was attributed to Cortisone, in one to the effects of suggestion, and in a fourth was mainly subjective and attributable to the feeling of well being caused by Cortisone. The fifth case (9) with intermittent attacks improved suddenly during the fifth month on placebo tablets and remained almost free from asthma during the observation period of three months. Cortisone was administered a month after relapse but was discontinued after three weeks because of severe depression. No improvement took place in this time.

Of the remaining ten cases treated with Cortisone but not with Placebo tablets good or excellent results were recorded in five, one of whom had had severe persistent asthma of two years duration prior to treatment. One other case of persistent wheezing in a severe asthmatic of twenty five years duration improved temporarily, but signs of heart failure due to cor pulmonale necessitated reducing the dose of Cortisone to 50 mgm. daily, which was below the effective level. This patient was considered to have some emphysema. Four of the cases who only had intermittent attacks responded satisfactorily.

Side effects
Side effects were not serious. One patient (9) became depressed, another (14) developed oedema and complained of feeling ill due to a 'bursting sensation' in her chest and face and a third (11) showed evidence of heart failure due to cor pulmonale. A fourth (16) had a cough facture of a rib after 2½ years treatment: it was considered that this might have been due to skeletal decalcification although this was not apparent radiologically. Fourteen patients who continued on Cortisone for three months or more increased in weight from 6 to 24 lbs. Three lost weight or increased by less than 2 lbs. One patient (1) who had responded well during three months on Cortisone in doses between 50 and 75 mgm. put on 15 lbs in weight. Three patients with good response had considerable intensification of asthma shortly after termination of treatment and two of these (1, 15) developed severe status within two weeks: one of them (15) was admitted to another hospital where Cortisone was not administered and died in the attack Cases who showed no response to Cortisone were not upset even by sudden termination of treatment.

Failure to respond on Cortisone
Details of the thirteen cases who responded only slightly or not at all are shown in Table 3. Four had emphysema (6, 7, 11, 14): two of these and one other had their treatment terminated or modified because of side effects (9, 11, 14). Two patients (5, 20) had nasal polyposis, one with chronic antrum infection Cases with persistent expiratory wheezing for periods of one year or more, even if not accompanied by definite evidence of emphysema, with one exception failed to respond to oral Cortisone therapy in the dosage employed by us. Three relatively mild cases of intermittent asthma (4, 10, 13) also showed no appreciable response.

Further possible reasons for failure to respond are considered in the discussion at the end of this paper.

The following case histories are typical. The first three responded successfully.

TABLE 3

Failure to respond satisfactorily on long term Cortisone

Case No.	Sex	Age	Lung damage	Persistent wheezing	Side effects	Weight increase	Duration of treatment	Average daily dose	Improvement but good or better response to Placebo
2	F	39	0	+	0	+ 6	6/12	70	0
3	F	44	0	+	0	+ 2	6/12	94	0
4	F	31	0	0	0	+11	6/12	82 5	+
5	F	40	0	+	0	+16	6/12	100	0
6	F	51	++	+	0	+ 8	6/12	70	0
7	M	41	++	+	0	— 1½	4/12	100	0
9	F	41	0	0	+		1/12		0
10	M	37	0	0	0	+14	6/12	95	+
11	F	49	++	+	0	— 1	6/12	73	—
12	M	37	0	0	0	+ 6	6/12	85	—
13	M	28	0	0	0	— 1½	6/12	95	—
14	F	32	++	+	+		2/52		—
20	F	49	0	+	0	+10	6/12	80	0

Clinical comments

2. Moderately severe asthma. Emotional factor present.
3. Moderately severe asthma Has never earned living because of asthma. Emotional factor present.
4. Emotional factor prominent. Moderately severe asthma.
5. Antrum infection intermittently for many years In hospital repeatedly with asthma. Emotional factor present
6. Considerable emphysema. Little evidence of infection.
7. Considerable emphysema. Little evidence of infection
9. Treatment terminated after one month owing to depression.
10. Improvement mainly subjective. Mild asthma only.
11. Initial slight improvement. Emphysema present. Large emotional factor. Has never earned her living because of asthma.
12. Moderately severe asthma.
13. A mild asthmatic Attack rate unaffected.
14. Treatment terminated because of bursting sensation in chest. Very severe asthmatic of long standing with evidence of lung damage.
20. Nasal polypi. Mild asthma with marked bronchitic tendency.

remained persistently dyspnoeic on exertion. Emphysema was present in this case The second patient was enabled to return to work and has remained relatively free from attacks for one year. The remainder were all considered to have responded well judging by their former state, but only one could be regarded as having remitted completely i.e. case 1 who had also responded well to Cortisone over a period of six months. Two others were enabled to lead almost normal lives though one (27) was temporarily incapacitated as a result of bronchial infection after one year. The remainder were all incapacitated to a greater or less extent.

Five cases have now been receiving treatment for 1 year or more.

Side effects

Side effects in this series were limited to increase in weight of 4 and 6 stones in two cases who presented the typical appearance of Cushing's syndrome although their asthma was incompletely controlled. One of these (21) had definite evidence of emphysema The other patients have increased in weight by amounts varying from 12–16 lbs. One patient (23) with a history of duodenal ulcer had a melaena.

Failure to respond to A.C.T.H.A.R. gel

One patient (26) responded only poorly to A.C.T.H.A.R. gel, a woman of 58 whose asthmatic attacks commenced at 45, diagnosed as severe asthma of undetermined origin with secondary infection. Nocturnal attacks had been present for some years, and recently had become worse with development of nasal polypi. Repeated attacks of bronchitis also precipitated severe attacks. She had been admitted to hospital in status at all times of the year on a number of occasions, and on two occasions responded to A.C.T H. when other treatment had failed. A radical ethmoidectomy was carried out in November 1954 with little benefit. Skin tests were negative. After admission in March 55 she was given A.C.H.T.A.R. gel 10 units on alternate days. As she became increasingly wheezy the dose was increased to 20 units daily, and then to 40 units daily. In spite of this her condition deteriorated, she developed heavy infection with Str. Pyogenes and Str. Pneumoniae and was again admitted in status after three months treatment. At her best this patient's vital capacity was well below the normal figure and persistent expiratory wheezing was present. It is probable that her lungs were the seat of organic change.

The following case histories are examples of the type of case treated.

Case 23: Male aged 47. Severe asthma of indetermined origin which commenced insidiously on holiday three years previously. Since then he had been almost continuously wheezy with severe exacerbations of his asthma. No precipitating

and had been bed ridden at home almost continuously, consuming large quantities of symptomatic remedies. He had responded temporarily to Cortisone in another hospital but he was said to have developed rigors which necessitated termination of treatment. He at once responded to A C T H.A.R gel the vital capacity rising from 1,400 ml to 3,000 ml within a few days Attacks of dyspnoea still occurred and an expiratory wheeze was usually audible on examination. His weight which was 8 stone when first seen increased to ten stones within a month. In spite of restricted salt intake it has further increased by four stones on continued treatment with 20–40 units of A C.T.H.A.R. gel daily during the subsequent eleven months. He now presents the characteristic moon face and high colour of Cushing's syndrome. Although he has not yet returned to work, it is felt that there is no real reason why he should not do so; he has not been confined to bed since his admission, and has had no attacks which he has been unable to control His asthmatic state is however only partially controlled in spite of well marked hyper adrenalism.

Case 27· *Male aged* 47. Intermittent asthma of bronchitic type. A detective inspector who had suffered from duodenal ulcer in the past and had had asthma for 25 years. He was a sensitive and nervous man whose attacks were precipitated by anxiety and bronchitis, attacks occurred at all times of the year but were more frequent during the winter months These had been mild and infrequent until

to lose no further time from work and as his ulcer had given no cause for trouble for some years, twice weekly injections of A C T H A R gel 40 units were given. These were soon reduced to 40 units weekly and for the next five months he remained free from asthma. He then had a melaena of moderate severity. While in hospital his asthma recommenced and at his own request A C.T H A R gel was continued with full ulcer therapy; the asthma responded dramatically, the vital capacity rising sharply. He remained well for a further nine months on doses

bronchitis with which he was laid up for several weeks. His weight increased by 10 lbs within a short time of commencing treatment and has persisted at this level, which is not excessive for his height.

Discussion

previously received

in-patients. The eight cases treated with A.C.T.H.A.R. gel are not comparable with the former group since all had been treated successfully with Corticotrophin as in-patients. Seven of these continued to do well as out-patients. Those patients who had been subject to bronchial infections continued to develop fresh infections from time to time while under treatment and early recognition of these played an important part in maintaining them in reasonable health.

Published results of treatment of ambulant asthmatics with oral Cortisone are shown in Table 4. Most authors have, however, carried out treatment for a few days or weeks only and have continued with long term treatment only in those patients who responded successfully in the first instance. Savidge alone has employed placebo controls.

TABLE 4

Ambulant Cortisone therapy	No. of Cases	Good or Excellent	Fair	Slight or None
Irwin et al	23	23	0	0
Savidge & Brockbank	13	6	4	3 including 2 deaths
Friedlaender & Friedlaender	17	12	2	3
Arbesman & Richard	63	41	15	7
Blumenthal	30	22	8	0
Schwartz, F.	22	16	0	6 including 1 death
Lowell[1]	19	17		2
Present Series	20	7	0	13

[1] Lowell describes 17 cases as 'satisfactory'.

The possible reasons for failure will be briefly considered.

Presence of organic disease of the lungs or of uncontrolled infection
Two patients (6 and 7) in the present series were considered to have had primary emphysema although this was not recognized at first owing to misleading histories. These cases should clearly not have been included. Two other patients (11, 14) treated with Cortisone were thought to have emphysema secondary to their asthma; one responded initially but the development of oedema and venous congestion necessitated a reduction in the dose of Cortisone below the effective level: the other complained of a 'bursting sensation' in the chest on 100 mgm. daily and

treatment was terminated within two weeks. Bronchiectasis affecting a small localised area of the middle zone of the right lung was present in one other (5) although there was no indication of persistent infection. Arbesman, Gay and others consider that emphysema or bronchiectasis are not incompatible with a reasonable response to endocrine substances. One of our patients (21) with wellmarked emphysema did indeed respond satisfactorily to A.C.T.H.A R. gel and when in status to intravenous Corticotrophin. Three patients (5, 20, 26) had nasal polypi two of whom had repeated antrum infection: all three failed to improve. Bronchial infection was a complicating factor in many of these cases, and recurrent infections were not prevented by endocrine treatment. Infection was in all cases controlled at the commencement of therapy.

Inadequate dosage

The dosage employed was similar to that used by most workers. If more than 100 mgm. of Cortisone or 40 units of A.C.T.H.A R. gel are given daily over long periods of time, serious side effects are likely to develop.

Inadequate absorption of Oral Cortisone

Friedlaender has pointed out that this may occur. He describes a patient who responded to I.M. Cortisone but who failed to respond to oral Cortisone. This may have accounted for failure in two of our patients (3, 13) whose weight remained approximately stationary during six months of treatment with an average daily dose of 94 mgm. and 100 mgm. of Cortisone.

Side effects

Treatment was terminated after three weeks in one patient (9) because of depression and after two weeks in another (14) who also had lung damage. In one case with emphysema (11) the dose of Cortisone was restricted because of oedema and evidence of cor pulmonale.

Emotional factors

Emotional factors were thought to have contributed to the maintenance of asthma in ten patients prior to treatment with Cortisone or Corticotrophin Five (2, 3, 4, 5, 11) failed to respond to Cortisone, but five (8, 16, 17, 21, 23) responded satisfactorily to Cortisone or Corticotrophin. There is therefore no evidence that emotional factors account for failure to respond in the present series.

It has not been possible to explain failure as the result of any single cause, and in a number of cases no satisfactory reason has been discovered. Although moderate lung damage is not incompatible with some improvement, the presence of fibrosis or emphysema clearly interferes with a satisfactory response. The recognition of such lung damage

is, however, not always easy even with the assistance of lung function tests, as Beale et al have pointed out.

Not only must we accept that a proportion of chronic asthmatics will fail to respond satisfactorily over a long period of time to Cortisone or Corticotrophin in reasonable dosage, but as Lowell et al have stressed few of the cases who respond well can be recorded as having fully recovered normal lung function. Attacks of asthma still occur from time to time, the tendency to acquire bronchial infections is unaffected and in many the vital capacity remains reduced or the expiratory rate is greatly prolonged. Only one (1) of our 27 cases, a man of 36 with severe intermittent attacks of 2 years duration could be regarded as having been restored to normal throughout the period of treatment with A.C.T.H. Two patients (one on Cortisone and one on A.C.T.H.) have been enabled to return to work but six are still not working; one of these is considered fit to work but has not yet decided to do so. Three others have lost less time from work than in the year before treatment.

Conclusion

The value of Corticotrophin or Cortisone as a long term method of controlling symptoms in chronic asthma is limited. In a mixed group of cases with longstanding symptoms many failures may be expected: these may be partly explained by the presence of organic changes in lungs or bronchi, side effects, or with oral Cortisone because of inadequate absorption The effective dose of Cortisone or A.C.T.H. varies considerably from case to case and does not appear to be related to the severity of the symptoms of asthma. Objective methods should always be employed as far as possible in assessing results. The use of placebo treatment will demonstrate that some patients apparently responding to the effects of Corticoids have in fact undergone spontaneous remission or improved as the result of suggestion. Side effects in the doses used have not proved troublesome except for the tendency to put on excessive weight: depression, heart failure and melaena occurred in one case each.

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INTRODUCTORY LESSON ON HORMONAL TREATMENT OF BRONCHIAL ASTHMA

by

H. J. TEN CATE

Prolonged treatment of asthmatics with adrenocorticotropic hormon

Although treatment of short duration with ACTH may be life saving in severe asthmatic state, a prolonged remission of the asthmatic symptoms is seldom observed.

Especially patients with severe continuous asthma, mostly belonging to the elder age group, where in all probability endogenous (endocrine?) causes are more important than exogenous (allergic) causes, are apt to relapse within a few weeks

An attempt at prolonging the treatment by one weekly intravenous slow drip infusion of ACTH in 5 per cent glucose solution succeeded only at a single patient.

Prolonged treatment at home by 6 daily intramuscular injections is not practicable.

The long-acting ACTH preparations seemed more efficient for prolonged treatment at home.

At the Chest department of the Groningen university clinic of internal medicine two long-acting preparations are used. The first preparation owed his prolonged effect to the binding at carboxymethylcellulose, referred to as ACTH-C. The other preparation owed his prolonged activity to the adding of zinc, referred to as ACTH-Zn.

Before using these preparations for treatment their effect on the blood eosinophils of asthmatics and normal persons were recorded and compared to the effect of ordinary ACTH of the same batch. Basic conditions, like at the Thorn test, were required.

According the effect on the blood eosinophils the long acting preparations have their strongest effect 8–12 hours after the injection. Their effect on the adrenals seems stronger than the effect of ordinary ACTH. The effect of the long-acting preparations on the asthmatic symptoms also was strongest 8–12 hours after the injection and disappeared within 24 hours.

The observation that daily injections of the long-acting preparations act stronger against the asthmatic symptoms as the injections of the double amount every other day agrees with this.

As prolonged treatment with ACTH may cause serious side effects we only submitted patients to it, when other measures and treatment

were unable to prevent disability or to prevent perilous attacks.

The treatment always started on the hospitalized patient, mostly after a short treatment with ordinary ACTH. After discharge the treatment was continued at home, under supervision of the out-patient department for chest diseases. The patients came once weekly, afterwards once in 2 to 3 weeks for reexamination and control.

Besides physical examination laboratory procedures were involved, like examination of sputum (eosinophils and Gram), urine (albumine, reducing substances and urobiline), plasma electrolytes and haematocrite, eosinophils, respiratory function, circulation time, weight.

To prevent or to correct shifts of the plasma electrolytes it was necessary to prescribe a low sodium diet and additional potassium chloride (2–6 g. daily).

Besides the effects on the asthmatic symptoms the stimulation of the adrenals resulted in the gaining of weight by fat deposition, moonface, acne, pigmentations. Edema was not frequent, no more was a rise of the arterial tension. ACTH preparations also are able to provoke allergic manifestations. We observed urticaria, Quinckes edema and dyspnoea at a few patients especially with the intravenous drip method of ordinary ACTH.

The next two tables serve to give an impression of our results with the two long-acting preparations.

Three patients received (hydro) cortison.

The 22 patients are divided into 3 groups, namely patients with exogenous asthma (exo-allergy) demonstrable especially for many inhalant allergens; patients with endogenous asthma, no allergens demonstrable as causes of asthmatic symptoms and a group with mixed causes, they demonstrated allergy to foods (2) and aspirin (1), but also demonstrated symptoms after elimination of allergens. Of the group endogenous asthma some patients experienced allergic symptoms but no asthma after sulfa and chinidine and ACTH, (treated with cortison), grass pollens (only rhinitis)

Some patients of the groups endogenous and mixed asthma demonstrated complications like cor pulmonale, bronchiectases, emphysema, often in combinations. Some of these patients repeatedly suffered broncho bacterial infections

A good result means no further hospitalizations were necessary. Only few patients demonstrated freedom of symptoms during periods of some months. A bad result means during treatment further hospitalizations were necessary. Most patients felt better during treatment than before.

To sum up our experiences on treatment with long-acting ACTH preparations at asthmatic patients:

TABLE 1

Groups	Number of pat.	Ages	Duration of treatment	Results		Died
				good	bad	
Exogenous .	4	15—25 y.	2—10 months	1	3	0
Mixed	3	44—65 y.	8—38 months	2′	1	1′
Endogenous	15	39—70 y	6—33 months	8	7′′′′	4′

TABLE 2

Duration of treatment	Number of patients	Results		Died
		good	bad	
2— 6 months	6	1	5′′′	3′
6—12 months	7	4′	3′	2′
12—24 months	5	4	1	0
24—36 months	3	2	1	0
36—48 months	1	0	1	0

1) Prolonged treatment necessitates low sodium diet and additional potassium chloride (2–6 g. daily).

2) During treatment broncho bacterial infections are no more frequent than before treatment at the same patients.

3) Daily injections of long-acting preparations cause better clinical results than the double amount injected every other day.

4) The daily amount of the long-acting preparations has to be adapted to the changing needs of the patients. Mostly a daily dose of 5–15 U. suffices.

5) Increasing eosinophilia rising to high levels (60 per cent–4000/mm^3) is often a precursor of aggravation of the asthmatic state.

6) Other therapeutic measure readily can be carried out during treatment: Hyposensitization, symptomatic treatment (antihistaminics), treatment with antibiotics and cardiotonics (digitoxine-digoxine).

7) Changing the 2 long-acting ACTH preparations may be successful

when the clinical effect of the used preparation has decreased. Changing into cortison also may be succesful when both long-acting preparations afford no longer effect.

Sometimes it was necessary to hospitalize the patient again and treat him with ordinary ACTH. Afterwards the long-acting preparations again were used with sufficient result.

8) Most frequent side symptoms of treatment were: gaining weight, moon-face, acne, pigmentations Less frequent were edema, and rising of the arterial tension

9) The results of treatment are not overwhelming. However it must be taken into account that only selected asthmatics were submitted to prolonged treatment who underwent several other treatments without success and whose prospects were bad.

The best results are scored in the groups with endogenous and mixed asthma. The lowest results in the group with exogenous asthma. Adrenocorticotrophic hormon insufficiently protects against allergens, although experimentally some protection seems to be afforded.

DISCUSSION

ANTI-HISTIOCYTIC AND ANTI-ALLERGIC ACTION OF CORTISONE*

by

LINO BUSINCO

modification of the lymphoid organs and particularly of the spleen. In this regard the lymphocytolytic action of cortisone is often mentioned. The detailed histological study permits to recognize that the negative action of cortisone on the lymphoid organs and particularly on the spleen is not exercised upon the lymphocytes, but upon the histiocytic component represented above all by the cells of the germinative centers In fact, a first microscopical examination permits to see a reduction of the cellular elements of these organs which have been treated with cortisone And in this reduction are comprised of course also the lymphocytes But the principal negative action is exercised, as we have now said, essentially

to the alterations of the histiocytic matrix

Being established that these histiocytes of the germinative centers have a part of the greatest importance in the production of the antibodies, it is clear that cortisone develops the antiallergic action in a particular manner, acting against the histiocytes of these centers The morphologic and functional alterations brought about by cortisone upon the histiocytes deranges at its basis the mechanism of the reaction of the antibody against the antigen And during this stage of cortisonian histiocytic suffering we have the best therapeutic anti-allergic results of the hormone

When the administration of cortisone is stopped, the histologic study reveals in the germinative centers a quick reconstitution of the histiocytic patrimony; this reconstitution can be observed clearly at the microscope in a surprising wealth of caryokineses By means of this strong proliferation movement the germinative centers return to their normal morphological constitution and the tissues get rid of the last cellular leavings Once regained the normality of the

larly in the allergic functions.

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Time and again it is amazing to observe how treatment with ACTH, administered by intravenous drip (possibly combined with aminophylline) will result in the disappearance—if only temporary—of a status asthmaticus or bronchial asthma. A long-term treatment is much more difficult and the result obtained less striking. Cases of chronic bronchial asthma—in which every form of specific treatment has failed—are bound to recur sooner or later in an equally severe form when treatment with ACTH is discontinued. Apparently, administration by intravenous drip has the advantage—as has frequently been observed—that good results are even obtained in cases in which courses of treatment with cortisone or intramuscular injections of ACTH have failed This is of special importance in the event of a third or fourth course of treatment, as the patient, recalling the striking results obtained previously, will be acutely disappointed when improvement fails to occur. We have frequently been struck by the fact that the patient, when administration by intravenous drip (a form of treatment which often is extremely unpleasant to him or her) proves difficult, is not relieved when the physician, at a loss what to do, proceeds to administer a larger dose by intramuscular drip and, finally, a dose of a preparation of ACTH having a prolonged action, requesting him instead to continue with the intravenous drip, as this method is more effective in his opinion.

We used the following methods in the long-term treatment employed in fifty patients over a 4-year period:

a) administration of 25 (or more) mgm of ACTH by intravenous drip once or twice weekly, if need be, combined with administration of aminophylline. An antihistaminic was given prior to the intravenous drip and 0.3 ml. of adrenaline was injected intramuscularly at the beginning of treatment to prevent possible allergic reactions,

b) treatment with varying doses of cortisone, and ACTH, administered by intravenous drip, once every 6 weeks. In addition, this opportunity was used to examine the blood sugar, urine, ECG, etc ;

c) treatment with cortisone, alternating with a course of injections of a preparation of ACTH having a prolonged action, likewise combined with ACTH administered by intravenous drip every 6 weeks, the examinations also being made on this day.

In view of the fact that this treatment was used only in almost hopeless cases, the results may be stated to have been highly satisfactory The patients, including those previously disabled, were almost always rendered fit for work again. Meanwhile, constant efforts were made to develop a specific therapy.

There were 5 patients with complications:

a) one patient with an insulin-controlled diabetes, who was given 3 courses of treatment with ACTH prior to the long-term ACTH therapy, which involved a temporary increase of these dose of insulin to be administered, although the longterm treatment did not result in aggravation of the diabetes;

b) three patients, who became pregnant during treatment, in whom several previous pregnancies had failed to produce any improvement of the asthmatic

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symptoms—the very reverse occurred—and in whom treatment was continued during and after pregnancy without giving rise to any untoward reactions,

c) a patient with silicosis, affected with bronchial asthma and subject to asthma-like attacks due to the silicosis, whose symptoms disappeared completely during the period of treatment. Being impatient, he discontinued treatment after one year, whereupon all the symptoms recurred in full force.

Of the patients treated by these methods, 5 died as the years went by.

1) One died from acute heart failure three months after treatment had been discontinued (this was a 25-year-old girl, who had previously been treated with pneumectomy, which operation was followed by the recurrence of asthmatic symptoms, which were more severe than those observed at any time in the past).

2) Suicide, committed by an older patient, who had been harbouring suicidal thoughts for several years prior to treatment, however.

3) Acute heart failure in a 13-year-old boy, whose father had continued treatment himself in view of the excellent results and had refused any examination

4) A severe and uncontrollable attack of dyspnoea in a 37-year-old woman, in whom treatment had been discontinued at the request of the family practitioner and also for financial reasons.

5) An acute, severe attack of dyspnoea, terminating fatally within a few minutes, in a 56-year-old man, in whom treatment had been considerably reduced owing to bronchopneumonia. The patient had shown symptoms of fatigue, coughing, increased expectoration and a markedly increased ESR for a long time previously. Treatment with antibiotics had resulted in the disappearance of these symptoms and so far there had been no signs of dyspnoea, so that small doses of ACTH were constantly administered, until a very acute, brief, severe attack of (cardiac?) dyspnoea caused the death of the patient

Those patients, however, who are restored to normal life from a state of constant illness and disablement make combined treatment with ACTH and cortisone a valuable addition.

ACTH, HYDROCORTISONE AND PREDNISONE IN THE TREATMENT OF BRONCHIAL ASTHMA *

by

UMBERTO SERAFINI and UBALDO DI NARDO

We first studied the adrenal response, as expressed in the behaviour of the peripheral eosinophils, to intravenous ACTH in three series of experiments.

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The second series was concerned with the duration of adrenocortical stimulation studied in two ways Firstly by varying the duration of the intravenous infusion from 2 to 8 hours with a fixed dose of 20 mgm. ACTH. We found that the longer the duration of the infusion the longer is the duration of the eosinophilic drop below 50 per cent.

On the other hand when the duration of the infusion is kept constant at 8 hours and the dose is varied from 5 to 20 mgm. the duration of the eosinophilic drop increases with the dose.

In the third series of experiments we studied the intensity of the adrenocortical stimulation and found that when the time was varied and the dose kept constant at 20 mg the intensity of the response depends directly on the duration of the infusion. But when the duration of the infusion is maintained at 8 hours and the dose varied, the intensity of the response is relatively independent of the dose.

In order to establish the adrenocortical response of asthmatic patients to ACTH, we subjected 15 such patients to Renold's 8 hour test. It was found that asthmatic patients react in the same way as normal persons. Moreover, in asthmatic patients the eosinophilic drop evoked by 12 daily infusions of ACTH or by prolonged treatment with cortisone differs in no way from that seen in normal persons.

Regarding the relationship between ACTH and ascorbic acid we found that when ACTH is given by intravenous infusion, there is an initial urinary loss of vitamin C which may exceed the amount administered. In a second series we found that adrenocortical stimulation, as expressed in the eosinophilic drop, also occurs in vitamin C deficiency However the response lasts longer and is more intense when the body is saturated with ascorbic acid.

This means that when ACTH is given therapeutically, ascorbic acid should be given as well for the double purpose of replenishing the Vitamin C lost in the urine and in order to prolong and intensify the adrenocortical response.

ACTH given either intramuscularly or by intermittent or continuous intravenous infusion, hydrocortisone and prednisone have produced better therapeutic results than can be obtained by any other method. We obtained favourable results in 85—90 per cent of our cases However, it must always be remembered that we are dealing with remissions of symptoms and not with cures.

We are convinced that in asthma it is indispensable to make detailed etiological studies in every case, sothat, when indicated, desensibilization can be undertaken with lasting results.

Symptomatic remissions obtained by the use of hormones may be total or partial, depending on the degree of reversibility of the underlying morbid condition. It should, however, be remembered that before we can judge a result to be negative, we must have assured ourselves that the preparation used is active and that the dosage has been adequate. We had to do this several times when using compound E of F. When ACTH is being given intramuscularly, we must also be sure that we are not dealing with a case of socalled ACTH resistance

Regarding the results obtained with ACTH given by the intermittent or continuous intravenous route, it can be said that though the percentage of favourable results is the same, the improvement is not as marked as with the intramuscular route. On the other hand the intravenous infusion has certain undeniable advantages over intramuscular administration Far smaller doses can be used, the onset

of relief is much more rapid and the dosage can be more finely adjusted. Obviously it is the only method in those rare cases in which ACTH given intramuscularly is inactive.

With hydrocortisone the dosage is particularly low and thus eliminates significant side effects, such as may occur with ACTH and cortisone. This makes it possible to continue treatment even for several weeks. Hydrocortisone is, therefore, particularly indicated in cases of ACTH allergy.

The recently introduced prednisone[1] must undoubtedly be regarded as one of the most significant advances in cortisone therapy. We have only used it in a limited number of cases and cannot therefore express a final opinion on its efficacy but in the cases we have studied, we found it markedly more active than cortisone and comparable with hydrocortisone yet significant side effects were less than with any other similar hormone We can report on 10 patients suffering from severe asthma of long duration, who were given 30 mgm. daily by mouth during the first days after which the dose was gradually reduced until a maintenance dose of 15 – 20 mgm was reached. Treatment lasted from 7—15 days. The results

poor result from a subsequent treatment with hydrocortisone. The period of remission is about the same as that achieved with hydrocortisone. The secondary effects were an increase in weight of some patients and insignificant changes in arterial pressure and in diuresis. In no case was glycosuria seen.

A comparative study undertaken by us of the eosinophilic drop induced by the oral administration of cortisone and prednisone showed that the latter produced an identical effect with only one third the amount Studying 10 normal persons, we found that in man one obtains the same eosinophilic drop as is evoked by 50 mgm cortisone, with 15 mgm. prednisone. These data, at our knowledge, are the first published in the world medical literature, concerning bronchial asthma.

Owing to the fact that the partial or total remission of symptoms depends, as we said, on the greater or lesser reversibility of the underlying morbid condition, we use ACTH and the cortical steroids as a test by which to judge the reversibility of the asthmatic emphysema In fact in cases of continuous bronchial asthma that can look like real emphysema, hormonal therapy, in adequate dosage, establishes whether the symptoms are reversable or definitely irreversable. Apart from its diagnostic value, this is of course of great prognostic and therapeutic importance.

Among the very large number of cases studied in recent years we have encountered only 6 cases of ACTH allergy that manifested itself as asthma or anaphylactic shock

It is, therefore, necessary to stress the practical importance of regularly testing the sensibility to ACTH whenever treatment is repeated.

The observation of one case in which 50 — 100 mgm ACTH given intramuscularly produced neither a clinical remission nor an eosinophilic drop, both of which were obtained by giving as small a dose as 2.5 to 5 mgm. intravenously, suggests

[1] Prednisone is the designation given to delta 1 – 4 pregnadine 17 alpha, 21 diol 3, 11, 20 trione by the Council on Pharmacy and Chemistry of the A M.A , which was previously known as metacortandracin

that intramuscular ACTH may be incapable of producing a metabolic response not because the adrenocortical response is insufficient but because certain conditions of the tissues prevent the ACTH from passing into the circulation. This might also explain the decrease in the efficiency of ACTH which is not uncommonly seen in subsequent treatments Possibly the hormone may be inactivated in the tissues when there is no clinical response or in those cases in which the intramuscular Thorn's test is negative, which would then not mean that there is an adrenocortical deficiency

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ANTIBIOTICS IN ASTHMA

by

JACQUES DUCHAINE

The discovery of penicillin and its commercial production at low cost, was heralded, around 1946, as one of the most important steps in the treatment of those two troublesome forms of asthma: the so-called intrinsic asthma and the atopic asthma with bacterial infection.

About the same time, a new technique of introduction of drugs into the bronchial and pulmonary fields by inhalation of aerosols was being widely experimented and the conclusions were that aerosolisation of penicillin was the most economical, effective and logical manner in which to bring the drug directly in close contact with the infected mucosa. From 1946 to 1949, much work on that line was done in most European countries and in the U.S A

If the immediate aim was the search of a more effective medium to neutralize the consequences of infection in asthma, a secondary, but all the most, very important idea was to put to an acid test our prevailing theories concerning the influence, whether toxic or allergic, of bacteria on the different forms of asthma.

To-day, after nearly ten years of experimentation, it seems possible to re-appraise the whole question and to verify if our hopes have been, even partially, fulfilled.

Is treatment by penicillin (injections, aerosols or per os) a worthwhile procedure in infective asthma? Have the results obtained with antibiotics given us a better insight in the probable mechanism of infection in asthma and the related diseases?

When the published results of antibiotic therapy are studied, one striking fact appears immediately, a fact that previously does not seem to have held the attention it deserved The authors can be divided into two groups· those who use what may best be named 'supportive measures' (mostly, aerosols of aminophyllin or adrenergic bronchial [illegible]

[illegible] aerosols of the antibiotic. Unfortunately, in some cases, it is not always clear which precise technique was used, but nevertheless in five papers, respectively by Prigal et al.,[8, 9] Farrerons-Có,[4] Findeisen,[5] Sangiorgi[10] and Duchaine[2] who specify their results statistically, it appears that 'supportive measures' (aerosols of broncho-dilators) were used in

conjunction with the antibiotics. All the patients thus treated can be classified as cases of secundary infected allergic asthma, chronic infectious bronchitis or intrinsic asthma. Out of a total of 424 patients, results were favourable in 343 (81 per cent) and unfavourable in 81 (19 per cent). Conclusions can best be summarized in the words of Segal [11]: 'Best results can be obtained if the bronchial passageways are patent; we employ aerosols of Vaponephrin or Aleudrin 1 : 200 preceding the neo-synephrin-penicillin aerosols'.

The opinions of those who do not use 'supportive measures' is at definite variance with that expressed here above. In only two papers, have we been able to find statistical evidence of the poor results obtained by penicillinotherapy when no broncho-dilator drugs are used simultaneously. Of 123 patients, treated by Engelster [3] and Prigal et al., [8] only 40 (32 per cent) had favourable results and 83 (68 per cent) were not relieved.

Segal, in another paper, [12] confirms this: 'Such therapy is generally disappointing'. Olsen [7]: 'Results have been temporary and disappointing in our cases of asthma'. Gay [5]: 'Penicillin and sulfonamides were equally useless to the majority of sufferers from an infectious type of asthma'.

At this point, it seemed logical to conclude that any or most of the benefit that could be derived from penicillin aerosols, should be attributed much more to the 'supportive measures' than to the bacteriostatic virtues of the drug

Therefore, we tried a modest experiment. During three months, all of those patients, to whom previously we would have prescribed a series of penicillin + adrenergic aerosols, were put to a course of exclusively bronchial dilator drugs (adrenalin + theophyllin), without penicillin or any other kind of antibiotics. At the end of the treatment and six months later, results were grossly assaied in terms of physical signs, presence or absence of sputum, of dyspnea on exertion, tightness of the chest, feeling of well-being.

Although, it is especially difficult to found an opinion on statistics which rely so much on the patients' subjective judgement, we may say that, all considered, results with adrenalin + theophyllin were practically equivalent with those obtained with adrenalin + penicillin. What seemed one of the characteristic influences of penicillin, the thinning of the sputum with its conversion of purulence, was as easely gained with theophyllin. As with penicillin, results were temporary and relapses followed more or less rapidly.

To what reasons must we ascribe the failure of a drug which has been revealed so powerful in other diseases? We can only speculate on this question and state the issues without answering them:

1) The bacteria responsible for the symptoms of infective asthma are not those, like streptococcus viridans, which we habitually find in the bronchial secretions and most of which are penicillin-sensitive. Maybe, we are in fact dealing with little known organisms or perhaps, viruses.

2) So called infective asthma is not due to bacteria, or it may be that the foci of infection are so deeply imbedded in the folds of the mucosa that the antibiotics cannot reach them.

3) In the so-called bacterial allergy, bacteria probably have much less importance than the lesions they have induced. We know that these lesions are irreversible, contrary to those due to atopy, which are reversible with rapid restitutio ad integrum once the allergens have been removed or neutralized. The accent here is more on the consequences of the cause than on the cause itself.

4) In atopy, it is most probable that infection (especially, infection of the nose and auxiliary sinuses) acts as a trigger mechanism. For this reason, antibiotic treatment is always started too late and is powerless to stop the consequences brought by the spreading of the inflammation to part or the whole of the respiratory tract

Is it to say that penicillin is useless in asthma? Far from it, and it is our opinion that it has a definite value against infection in a closed cavity. If pulmonary abcess is rare in asthmatics, infection of the auxiliary sinuses is a very common complication of respiratory atopy and penicillin is very effective against it, especially in children.

Although, the newer antibiotics (tetracycline, chloramphenicol, erythromycine etc.) should be used in well defined circumstances (whooping-cough, pneumonia, pulmonary abcess etc.), I do not believe that they have been tried on any large scale, in ordinary bacterial or in infected asthma The price of these drugs is still prohibitive and they may not be devoid of dangerous reactions if given for a long period.

The new French antibiotic, *Framycetin*, obtained from Streptomyces Descaris, [13] has, in vitro, a broader spectrum of action than penicillin or streptomycin. It is, at present times at least, very active against most strains of staphylococci, but it is too toxic to be injected and must be used locally or by aerosols. From a very limited experience, I can say that it does not appear to give any better results than penicillin and it seems to be more irritating to the respiratory mucosa. It is still in the experimental stage and the only results yet published have been those of A. Biron, [1] with 36, good, 6, fair and 2 unfavourable results out of 44 cases; but, according to the author, 3 or 4 drops of Aleudrin 1 : 100 solution were added to the antibiotic.

Complications with penicillin are rare but should not be dismissed too lightly. Five or six years ago, penicillin aerosols often provoked

lesions of an irritative nature in the mouth or the pharynx (black tongue), but these were due to an imperfect purification of the drug and they are now very rare. On the other hand, I have been witness to a fatal case in a man, 45 years of age, sufferer of intrinsic asthma for the last twenty years, who died within five minutes after the injection of 1 million units of procain-penicillin. As this patient was known to be aspirin-sensitive, it is probable that the generalized shock was due to a latent sensitivity to the procain (or, para-) radical and not to the penicillin itself.

At this point, it is important, once again, to sound a word of warning. There is no doubt that fungic antibiotics and specially, penicillin are used without discrimination. Although they now appear to be harmless enough, we do not really know what changes they may bring about in the organism of patients who have been submitted, year in, year out, to this therapy. In my practice where most pollensensitive patients are routinely tested with 36 different fungi extracts, I find an increasing number of positive reactions to extracts of penicilium notatum, reactions without clinical significance, at least, at the present time, but what may happen in the future is unknown.

Another point which we should bear in mind is that neither penicillin nor streptomycine are potent enough to sterilize, even for a short time, the respiratory tract. Antibiotic therapy is only indicated if we can be reasonably sure to kill right off the most noxious bacteria. The danger of favouring the appearance of penicillin-resistant strains is a real one. although little experimental work has been done on this line in asthma.

What is the present status of the problem of antibiotics in asthma? I hope that many of our colleagues from different countries will be able to give their opinion on this question. I can only tell you how I feel about it. Clinical work on asthmatics is a specially time consuming procedure and we really should not appraise our results unless the patient has been under observation for at least one year while he undergoes the stresses of daily life in both its favourable and unfavourable circumstances.

Last year, impressed by the fact that congestion and inflammation are the main injurious symptoms in asthma, I used mainly hydrocortisone *or ACTH in conjunction with the better tolerated and most active sulfon*amides (gantrisin, elkosine or supronal). At that time, these antibiotics were prescribed to avoid any spread of the infection which could have been brought about by the hydrocortisone. The ease of this procedure, which does not need any injections, is, among others, one of its strong points. Results in cases of atopy with infection were strikingly good when used in combination with ordinary desensitizing measures; in

infective or intrinsic asthma, results were much less favourable, although somewhat better than with penicillin. But relapses were frequent and the sulfonamide-hydrocortisone therapy tended to wear off its effects as courses had to be repeated.

This year, my tendency is more or less to do away entirely with antibiotics (penicillin or sulfonamides) and use hydrocortisone alone. It is too early yet to conclude from a limited experience, but again I must emphasize the fact that if atopic patients do very well on such a therapy, results in the long-standing cases of chronic infectious asthma are far from good. Rational therapy of these lies still in a treatment consistant with the needs of the individual patient and where vaccination, hydrocortisone and antibiotics can all play their part.

Conclusions

1) Antibiotics should be used in well defined and limited cases where there are signs of localized infection (pneumonia, broncho-pneumonia, bronchiectasis, pulmonary abcess, infection of the sinuses etc.) and not in the forms of protracted bronchial congestion.

2) An effective antibiotic is still to be found for those cases where infection of the upper respiratory tract acts as a trigger mechanism

3) As far as we know, hydrocortisone alone or used in conjunction with antibiotics is the most effective therapy of infection in asthma.

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ANTIBIOTIC TREATMENT IN ASTHMATIC PATIENTS WITH BACTERIAL BRONCHITIS

by

J. MULDER

Bacterial muco-purulent bronchitis is often observed both in the acute and in the chronic form in asthmatic patients. The bacterial flora is the same as in the non-asthmatic group. The table shows the distribution of this bacterial flora in 296 cases of acute and chronic muco-purulent bronchitis, including asthmatics and non-asthmatic patients.

TABLE I

Incidence of the bacterial flora in 296 cases of acute and chronic muco-purulent bronchitis (combinations are left out)

H. influenzae	76 per cent
Pneumococcus	25 per cent
Neisseria	8 per cent
Staphylococcus aureus	5 per cent
Klebsiella	4 per cent
Escherichia coli	3 per cent
Streptococcus viridans	2 per cent

In about 80 per cent of the cases of chronic muco-purulent bronchitis (for the most part associated with bronchiectasis) we found symptoms of asthmatic bronchitis (e.g. sputum eosinophilia).

If in an asthmatic patient the bacterial flora is eliminated by antibiotics, the patient continues to expectorate sputum in which the neutrophylic leucocytes for the most part are replaced by eosinophils. The result of antibiotic treatment on the asthmatic condition in general is not very great, though marked improvement may follow, especially in acute cases Some asthmatic patients suffering from chronic muco-purulent bronchitis may even get worse and show heavy asthmatic attacks. In some way the chronic bacterial inflammation interferes with the tendency to bronchospasm. The explanation of this fact is not clear. Most patients, however, feel much better after the elimination of the bacterial inflammation because the quantity of sputum diminishes considerably and the chronic intoxication ceases. Unfortunately the bacterial inflammation relapses very often after some weeks or months, especially in cases associated with chronic anatomical bronchial changes (stenosis and bronchiectasis).

Inflammation caused by H. influenzae can be eliminated by 4 million units of penicillin per day (1 million units every 6 hours).

The combination of penicillin and streptomycin (0.5 g every 12 hours) is preferable, and it is probable that with this combination less penicillin is necessary. Streptomycin alone shows a failure in about 50 per cent of cases owing to bacterial resistance. Chloramphenicol and the antibiotics of the tetracyclin-group are effective in a dosage of 2 g per day. We treat most patients for a period of 10 days.

In acute pneumococcal infections a treatment with 300.000 to 600 000 units of procaine penicillin is sufficient. Chronic pneumococcal infections are very rare in asthmatic patients. Acute pneumococcal bronchitis however is rather common

DISCUSSION

P J VAN DER WERFF

I was much impressed by Prof. Mulder's lucid demonstration of several problems in the field of bronchobacterial inflammations relating to bronchial asthma and by his very thorough and accurate investigations and his accordingly highly reliable findings.

For a long time, we, in the Amsterdam Clinic of Allergic Diseases, have made grateful use of all advice on his own special method of investigation of the sputum [1] and on therapeutic measures [2]

With permission, I would ask Prof Mulder three questions:

1) What is your opinion on the possible causes of the phenomenon, mentioned by you and also observed by myself, viz. a severe bronchospasmodic aggravation which occasionally occurs when antibiotics are administered prior to anti-allergic treatment in chronic bronchial asthma with secondary bacterial inflammation?

2) Do you think that there is a probability of a primary origin of broncho-bacterial asthma, and if so, do you have objections to the initial administration of antibiotics in these cases?

3) Do you believe that there is usually an underlying, latent (i e. non-manifest) allergy?

J. MULDER

1) I do not know for certain which mechanism accounts for the fact mentioned by Dr. van der Werff Perhaps a cause might be that bronchospasm is counter-acted by the inflammatory tissue reaction in the submucosa and smooth muscles of the bronchi Every inflamed smooth muscle tends to lose its tone, causing dilation of the hollow organ to which it belongs.

Another hypothesis, brought forward by Dr. Orie in Groningen, is that the inflammation causes a stress reaction associated with more ACTH production.

2) & 3) I have the impression, but no proof, that some asthmatics start their disease after sinusal or bronchial infection caused by viruses or bacteria, but only when there is an underlying latent allergic tissue condition.

H. COLLDAHL

I would draw attention to the fact that in many cases of asthmatic bronchitis the bronchial secretions, taken by bronchoscopy, are sterile. Further I think that the pulmonary tissue in asthmatics must have a particularly high resistance against bacterial infections. How can this be explained by the bacterial findings of Mulder, I should like to ask how this discrepancy can be explained.

[1] References a.o MULDER, J. Thesis, Groningen, 1937; *Ned. T. v Geneesk. 92*, 3521, 1948.

[2] PLAS, M C. VAN DER, Thesis, Leyden, 1951.

J MULDER

The pure asthmatic sputum is sterile, which can also be shown by carefully washing the flakes in buffered saline and studying the strains. The discrepancy between the frequency of bronchial infections and pulmonary infections in asthmatic patients can easily be explained because H influenzae causes only bronchial infections and not, or only very rarely, pneumonia, and the serological pneumococcal types in bronchitis are generally of the higher types of Cooper, which do not readily invade the lungs.

ACTINOMYCIN C IN THE TREATMENT OF ASTHMA*

by

LINO BUSINCO

The eminently lymphotrope action of actinomycin on one side and the relations existing between the lymphatic system and immunity on the other side, have led us to the research of a possible influence of actinomycin c (Sanamycin) both on anaphylaxis and on the allergic syndromes The research has revealed that actinomycin c does not succeed in avoiding the mortal crisis which befalls the guinea pig as a consequence of the re-injection of albumen However, it has revealed that in the animals treated with actinomycin c the crisis has had a longer duration

On the contrary, actinomycin c has exercised a favourable influence on human allergy. The treatment by means of daily intravenous injections of small doses of [illegible]

2 times, once poor and once null. In a case of colitis the result has been only poor. We have had favourable results even in cases of inveterate and rebellious bronchial asthma; in chronic urticaria they have been at times surprising.

The doses we have administered have not brought about any trouble, with the exception of some transitory gastro-intestinal pains. However, in the guinea [illegible]

Regarding the details of our observations, the following must be emphasized.

In the guinea pig the fur often presents a certain brittleness and the single hairs fall easily off The gall bladder is often considerably dilated, and at the post mortem examination it is found to be inflamed Contrarily to what has been stated by other Authors, the number of the red and white blood cells has not undergone any important changements. At this point it is necessary to emphasize that the decrease of the number of the eosinophils which has been observed in the allergic patients treated with Sanamycin, is in perfect agreement with the favourable results obtained by this treatment.

Attention must be drawn quite particularly to the results of the electrophoretic examination of the plasma proteins The researches which have been performed

* From The Institute of Medical Semeiology, University of Rome.

on the guinea pig as well as on allergic patients demonstrate that the treatment

the following interpretation: by acting on the lymphoid tissue which is in charge of the formation of the antibodies, actinomycin C deprives it of this important function

ment which is usually to be observed in the allergic patients under the effect of Sanamycin. By diminishing the rate of antibodies, the treatment deprives the antigens of an important part of the material upon which they react: therefrom the improvement of the clinical condition.

ANTIBIOTICA THERAPY

by

HELGE COLLDAHL

When one has to decide in a case of asthma if antibiotica therapy ought to be given, the first question is this. is there any infection present or not? According to an

before yesterday,

ot found to have

lungs.

Asthmatic patients with elevated BSR had bronchial infection more often than persons with healthy lungs An elevated BSR is according to my opinion the best sign of a complicating infection.

collected by catheterisation through a tracheal tube under general anesthesia with Evipan and Scoline. I think that this method is the most exact one to employ when investigating as to whether bronchial infection is present or not. With this method a differential count of the bronchial secretion will give further evidence of the presence of a bronchial infection. In this case neutrophilic leucocytes are often in excess even if a marked increase of eosinophils is present. When no infection existed, eosinophils were found preponderant in the secretion In all infected cases there was mucopurulent or purulent sputum, but in most cases

skin test there is in the bronchial secretion often an enhancement of eosinophilic leucocytes indicating in all probability that allergic factors are of significance although the antigen is unknown. As the eosinophils specially are in excess when no bronchial infection exists it is unlikely that the antigen in these cases is of bacterial origin. A possible explanation might perhaps be that the antigen is formed from destroyed bronchial tissue.

We found bacterial infection in our asthma material in 25 per cent of the cases examined.

When suitable antibiotics are administered to asthmatic patients with bronchial infection, the asthmatic troubles often become aggravated. In such cases a combination with antibiotics and ACTH is indicated.

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FURADANTIN

A NEW ANTIBACTERIAL AGENT IN INFECTIONS OF THE RESPIRATORY ORGANS

A preliminary report

by

H. CHR. PAULSEN

1) The bacterial flora in infections of the respiratory organs present great variations, and the treatment results are to a high degree dependent on the resistance against antibacterial therepy of the bacteria concerned in each case.

2) In most [illegible]

[illegible]

tract

3) In 1944, Dodd and Stillman found that certain furan compounds could be given new antibacterial properties by addition of a nitro-group to the molecule Thus we got a new preparation—Furadantin (nitrofurantoin)—which was found to have a broad antibacterial spectrum, with very rare occurence of acquired resistance, and with low toxicity.

4) Furadantin is a yellow, crystalline substance soluble in water. It is resorbed quickly and almost completely from the intestine. Even in the case of large doses, the blood concentration has been found to be low (Palmløv and Tunevall), and the preparation has therefore been of no importance in infections of the respiratory organs.

5) The nitrofuran derivatives attack the bacteria by destroying certain enzymatic processes necessary to the vital functions of the bacteria. The mechanism is evidently of a different character from that of sulfonamides and antibiotics, which involves that acquired resistance against the latter agents does not make itself felt in the use of the [illegible]

[illegible]

6) The antibacterial spectrum of F[illegible]

[illegible]

7) In vitro has been found that strains of staphylococcus aureus, streptococcus mitie, streptococcus pyogenes and Escheria coli showed no tendency to permit development of resistent bacterial strains (shown by Mintzer, Kadison, Schlaes and Felsenfeld at Hektoen Institute for Medical Research, Cook Country Hospital, Chicago) and Grayson Carroll gave in February, 1955 information of staphylococcus sensitive to Furadantin in 44 strains, none resistent.

8) Originally I started this work as a new treatment of Proteus vulgaris, which is a frequently occuring microbe in chronic nose affections and rhinitis, and it is found not infrequently in our asthma and emphysema patients with chronic bronchitis, ectasis, fibrous pulmonary changes with major mechanic obstructions, and protracted retensions. It is also found in patients that have been subjected to intense penicillin treatment. It is found almost exclusively in adults—especially elderly people—and I have never found it in children. Dick Henriksen found the Proteus vulgaris group in 5 per cent of a material consisting of 180 cases in his work intitled 'Studies on the bacterial flora of the respiratory tract, in acute and chronic bronchitis, bronchial asthma, and lunggangren' (1937) and 5,7 per cent in the group 'chronic bronchitis, bronchial asthma'. This group further contained:

Pneumococcus	12,5%
Staphylococcus albus	16,3%
Staphylococcus aureus	19,2%
Haemophilus influenzae	7,7%
Streptococcus	63,5%
Escheria coli	43,0%
Klebsiella	10,0%

Haemophilus influenzae is very sensitive to Furadantin and, on account of this, *used as testbacterium.*

9) Streptomycin treatment has rendered good service in cases of Proteus vulgaris, but it has not always given satisfactory results It therefore seemed natural to try a nitrofuran preparation, considering the good results that had been achieved with this agent in cases of Proteus in the urinary tract, but the obstacle was the low blood concentration that was possible to obtain and that did not produce any effect in infections of the upper respiratory tract and the lungs The only possible way of obtaining a satisfactory effect was then to use Furadantin in local treatment with aerosol, various solution strengths (produced in co-operation with the A. B Pharmacia, Uppsala, Sweden) have been tested, and the experiments are going on.

Furadantin has been combined with Tween 20 (polyoxietylensorbitanmonolaurat) which has no antibacterial effect, but its physical activity are a liqurfying effect and lowering of the surfacetension, both of value in the treatment with Furadantin —and antibiotics too—which reach the bacterium easier and with better effect, and perhaps have some influence on the tendency of resistance.

The side effects were insignificant; 1 out of the 38 patients subjected to this treatment showed symptoms of nausea, but it was not necessary to interrupt the treatment. Other side effects mentioned in the literature are emesis, and one isolated case of skinhypersensitiveness, which disappeared after removal of the

preparation, but the doses used in aerosoltreatment are very small in comparison with that of infection in the urinary treat. Until further experience is gained it is advisable to check the blood during the treatment. In my cases no blood change has been proved.

10) *Case I* was a male of 55 years with fibrous top changes and planigraphic actasis in the right side, where strong growth of Proteus vulgaris and staphylococcus aureus were found, both sensitive to streptomycin, chloromycetin—and staphylococcus to penicillin too. The patient was treated with streptomycin 15 grams and chloromycetin 15 grams and penicillin without effect. Renewed test during first 32 days revealed continued strong growth of Proteus vulgaris and staphylococcus aureus with positive plasma coagulase reaction. Aerosol treatment with Furadantin solution was begun, and after 7 aerosol treatments, there were no longer any proteus vulgaris nor staphylococcus aureus to be found—and the patient became afebrile. Test after 5 months showed that there was still no growth of Proteus vulgaris nor staphylococcus aureus.

11) *Case II* was a male of 44 with asthmatic bronchitis. Culture of the expectorate revealed growth of Proteus vulgaris—sensitive to chloromycetin, terramycin and sulfatiazol. He was treated with terramycin, but the treatment had to be discontinued because of allergic reaction. He was then treated with Streptomycin, penicillin and thyrosolvin inhalation (6) with positive effect. He had a relapse a month later, and was given aerosol treatment with Furadantin solution, which removed the symptoms. 3½ months after the end of the treatment, there was still no Proteus.

12) *Case III* was a male of 65 with asthmatic bronchitis and rhino-sinusitis (vaso[illegible]
sinus [illegible]
both [illegible]
ment was resorted to all the same, and the patient reported improvement of the rhinitis after two treatments,—after the third treatment negative physicals above the lungs and improved respiration. After 7 treatments there was still profuse growth of [illegible]
sinuses, it [illegible]
from the n[illegible]

13) I started this work with treatment of infections of Proteus, but it was very soon proved that Furadantin had a good effect on other bacterial pulmonary infections—in some of these cases antibiotica had had no effect—and after [illegible]

[illegible]

of increasing infections due to antibiotic resistance. Here staphylococcus aureus is the most typical illustration.

14) Infection with penicillinresistant staphylococcus aureus increase now as a consequence of the antibiotic treatment. From a series of hospitals all over the world reports have been given of strains of staphylococcus, which exist inside the hospitals, are resistant to penicillin to a greater extent than staphylococcus outside the hospitals.

Publications 1943—44 revealed about 12 per cent of resistant strains. In Copenhagen Erna Lund demonstrated an increase from 16 per cent in 1947—48 to 59 per cent in 1949—51. Laurell and Wadmark found in 1953 staphylococcus isolated from patients at a pediatric department 68 per cent and from the hospital staff 83 per cent staphylococcus resistant to penicillin. In some departments of the Epidemic Hospital in Stockholm practically all the staff had staphylococcus aureus resistant to penicillin. When we know that staphylococcus have resistance to streptomycin, aureomycin and terramycin up to 45 per cent, we may say that it is a dangerous development. Strains of resistant staphylococcus aureus are now one of our great problems.

It appears to me that Furadantin offers much promise for the treatment of bacterial infection in the respiratory tract, through its effectivity and lack of resistance to staphylococcus aureus It seemes that Furadantin is to prefer to the large doses of penicillin and streptomycin mentioned today.

The preliminary results arrived at induce to continue the work, and the results will be reported later.

FOCAL INFECTION AND ALLERGY

by

H. A. E. VAN DISHOECK

Local inflammatory processes affect more or less markedly particularly in the acute phase, the entire organism. When the local inflammation is chronic—either with or without exacerbation—it is called an inflammatory focus. These focal infections may follow a course without, or practically without, local and general symptoms. It is generally believed that such inert foci are nevertheless capable of setting up serious morbid symptoms in remote organs. Diseases mentioned in this connection are, inter alia, the collagen affections such as acute and chronic articular rheumatism, neuritis, iritis, nephritis, endocarditis, myalgia, chorea, and some forms of asthma. The foci may be present in, inter alia, the tonsils, the secundary nasal cavities, the teeth, the gallbladder, the pelvis and the intestine. With regard to the manner in which the infection focus may cause such diseases, as arthritis and asthma, various assumptions suggest themselves.

Bacteriaemia

In the first place the germ might pass from the focus into the bloodstream, and thereby provoke a temporary bacteriaemia and toxaemia. This is the idea which Osler formulated when calling the tonsils the 'porte d'entrée' for rheumatic infection Also Billings stated that clinical observation had demonstrated the existence of such temporary bacteriaemia beyond all doubt. Direct proof of this type of bacteriaemia, however, is difficult. But there is one observation that argues in favour of its existence, i.e. the fact that following tonsillectomy, bacteria were found in the blood It is further known that, in cases of articular rheumatism, an attack often occurs after tonsillectomy. In such cases, therefore, we have both bacteriaemia and attacks. This clearly suggests the conclusion that an invasion of bacteria was the actual cause also in former cases of angina followed by an attack

In all diseases in which bacteria are found in internal organs, and in which invasion, either in continuity or via the lymphatic system is impossible, as in endocarditis, transport via the bloodstream must be assumed. Invariably, the question will then be at what point the bloodstream was infected. The rational reply to this question will have to be that the infection most probably occurs at the point where there exists an inflammatory focus and where, therefore, the bloodstream and the

bacterial flora are in close contact. This is the case f.i. in the tonsillar crypts, in an infected regional lymph gland, or in a dental abscess. In particular, one should here think of an infected thrombus as the cause of the germ's passing into the bloodstream. In accordance with this conception Bolck and Arndt found in 57 out of 70 tonsils of rheumatic patients, deeply penetrating into the peritonsillar tissues, severe chronic inflammation often accompanied by phlebitis.

This conception of a metastatic infection or mild sepsis, therefore, implies that the bacteria, coming from the focus, nestle either temporarily or permanently in the remote organ, and may, therefore, be cultivated from the diseased organ, as in endocarditis. Presently the conception that endocarditis lenta should be a weakened sepsis caused by streptococci 'tamed' by their host, cannot be maintained. The investigation of Griffith and Lancefield learned that the pathogenety of the streptococcus is linked to its chemical and immune-biological properties. Thus the streptococci of the polysaccharid containing A-group are the cause of angina, scarlatina and erysipelas, whereas endocarditis lenta is caused by the milder viridans group.

In asthma, notwithstanding the vaccin therapy which is based on the assumption that bacteria or their products enter the bloodstream, such a mild sepsis is never proved.

Toxaemia

In the second place it is thought possible that, although no living germs may pass into the bloodstream—or that, if they do, they will soon be killed—but that their toxins and decay products definitely do enter the circulation This re-absorption of bacterial products, chiefly via the lymphatic vessels, is probably a continuous process whose intensity depends upon the activity of the focus.

A wellknown example of the direct toxic action of a bacterial focus on a remote organ is diphtherial myocarditis, as Billings already stated to support his argument.

In asthma as well as in rheuma such a re-absorption of bacterial proteins is very probable, but the tissue-damage caused by these products is not so marked as in diphtheria.

Allergization

Allergization of the organism by bacterial products is a widely known phenomenon. It must be assumed that, against foreign protein re-absorbed parenterally, immune antibodies will be formed in the body. These processes have been studied with both clinical and experimental accuracy with respect to, e.g. tuberculosis and rheumatic fever. In addition to immunization, however, there is also sensitization. These

two phenomena, although both allergic in nature, must nevertheless be viewed as separate entities. It is precisely in diseases caused by focal infections that sensitization, and the reactions caused by it, are prominent and of the utmost importance for our understanding of bronchitis and asthma.

Animal experiments to imitate allergic tissue changes

An example of a disease which is even more than asthma thought to be due to an infection focus is articular rheumatism. Countless experiments have been made in the course of the years in order to provoke this affection in animals, with the aid of the bacterium that causes it in man. These experiments have not been entirely successful, although it has proved possible to produce formations closely resembling Aschoff's nodules. This effect was obtained by the repeated infection of the animal with streptococci A single infection might perhaps kill the animal, but never produced the effect in question Thus a prelimary sensitizing infection is obligatory for the allergization of the animal. In addition, these experiments are only successful in a limited percentage of laboratory animals In others—for reasons as yet unknown—the disease fails to develop, a fact which is analogous to the human form of the affection The observation of Murphy and Swift that, in the positive cases, there is hypertrophy of the adrenal cortex, points to the correlation of these diseases with that organ. Pagel has pointed to the two fundamental pathologic-anatomic symptoms in allergy, viz,

1) in the presence of much reagin and allergen: oedema, bleeding, and necrosis, i e. the phenomenon of Arthus.

2) in the case of less violent and more prolonged action · granulomatosis. The Aschoff's nodules belong to this latter group.

The Shwartzmann phenomenon

In this respect the Shwartzmann phenomenon is also important. Shwartzmann showed that, by first injecting the skin of a rabbit with a bacterium-free filtrate of a culture, followed by a second, intravenous, injection of the same filtrate, he produced local necrosis. This proves that bacterial products are capable of sensitizing a tissue, and that the supply of the allergen through the bloodstream can produce a reaction. Later on, another, extremely important observation by Shwartzmann and Sanarelli was added to this; viz. that the second, intravenous injection need not even be of the same culture. To provoke such a hetero-allergic reaction, requires extremely sensitive animals, and a large quantity of filtrate This reaction is far less frequently successful than the specific one.

Recently Thomas and Stetson have provoked the Shwartzmann phenomenon by producing focal infections with haemolytic streptococci

in animals, followed by the injection of a number of bacterial toxins. They then observed the occurrence, in a number of laboratory animals, of a generalized Shwartzmann phenomenon, consisting in haemorrhagic necrosis near the foci, bilateral necrosis of the adrenal cortex and cardiac lesions strongly resembling rheumatic affections. This type of experiments has given the focal-infection-theory a sound experimental basis.

Organ localization

A third series of experiments is also of great importance for the proper understanding of focal infection in connection with its localization in particular organs. The basal phenomenon was described by Auer, who found that, when a sensitized animal had been brought into a state of protracted shock by sub-lethal injections of allergen, an intensive phenomenon of Arthus could be produced by rubbing xylol into the animal's ear. Kümmel gave the first sensitizing injection into the eye, and found, upon re-injection through the bloodstream, that the reaction was localized in the eye. Even an injury alone is enough to produce a localization of the reaction in the injured organ, Thus, nephritis may be provoked in an animal sensitized to a serum foreign to its species, by a second injection in which a special nephrotoxin has been added to the serum. Kallos' investigations have shown that, in an analogous manner, localization in the heart can be obtained by means of caffeine, while, according to Vaubel, cooling can have a similar effect on a joint.

Clinical consequences

The over-enthusiasm as well as the waning enthusiasm of physicians to remove all tissues that might possibly harbour pathogenic germs must be attributed to lack of proper knowledge of the problem. It is undeniable that there are distinctly successful cases but it is necessary not to pitch one's expectations too high. We are, in fact, justified in concluding, on the ground of animal experiments and clinical observation, that an infection focus sensitizes the body, and that the re-absorption of bacterial products may act as an intravenous re-injection. Whether such a re-injection will result in an attack cannot be predicted, either in animal or in human cases. Any reaction will preferably occur in an organ which had already passed through an infection by the germ, or which had been injured in some other way. There is no doubt that these processes are far more complex than we can realize on the ground of our present immunological knowledge.

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if an infection focus that was probably the initial cause has been done

away with, it is nevertheless possible for other bacterial products occasionally to arrive in the bloodstream from other places, and to provoke fresh attacks. *It is also possible that the primary focus has already done* so much damage that repair and recovery turns out to be impossible even after removal of the focus Finally, it should not be forgotten that causes other than allergic ones may be partly or alone responsible for the diseases in question.

There exist statistics showing the favorable effect of the removal of infection foci; but other statistics, too, have been published which deny both its preventive and its curative effect These statistics are open to *considerable criticism* Thus, it is illogical to compare the group of operated cases with the group of unoperated ones, and to state that the percentage of attacks is equal in both groups. For, the former group naturally comprises the most serious cases, as well as those in which a focus has produced chronic intoxication and sensitization for a long time, but in which the symptoms had not yet become manifest. These, after all, are the patients with local and general symptoms of infection. In such cases it is even possible for the first attack to occur directly after the removal of a focus. This fact is then used—wrongly, in my opinion—as a powerful argument against operating, whereas it is, to a much greater degree, an indication of the causal connection between the focus and the systemic disease. Such a post-operative attack, however, should be prevented by performing the operation under protection of antibiotics.

Focal infection and asthma

The number of asthma patients in whom the first attack followed upon an infection of the respiratory passages, is considerable. This fact alone already points to the connection between bacteria and asthma If there are patients in whom a non-allergic bacterial toxaemia may be assumed to be the cause of their attacks, is doubtful. But if we assume, also here, the existence of allergic sensitization by bacterial products, and apply our knowledge concerning these products, the focus theory assumes a different aspect. For, in asthma as in arthritis, the chief objections against this theory were that (*a*) removal of a focus often turned out unsuccessful, and that, conversely, (*b*) there may be attacks in the absence of a demonstrable focus. Harley pointed out that it is impossible in some cases to do away completely with a focus, but that the principal reason for this failure must be sought in the non-specificity of the nucleo-proteins. When, for instance, a streptococcal focus in the tonsils, which has caused the sensitization, is removed, it is possible for re-absorption of nucleo-proteins, maybe of another group, to continue from another place, for example from the nasopharynx. This is one explanation based on the non-specific Shwartzmann phenomenon.

Recent investigations have shown that probably it is not so much the bacteria in the patient's infection focus that constitute the danger to him, but rather the foreign groups with which he is infected. Quite possibly, in such an acute, new infection the re-absorption is more intense than from an old, closed-up focus

A recent objection against the focus-theory is that the antibiotics capable of sterilizing the body fail to cure this bacterial sensitization and stop the attacks. As against this, one may argue that (*a*) sensitization is an existing condition which is not changed by antibiotics; (*b*) re-absorption of dead bacteria can continue for an indefinitely long time; (*c*) re-infection is a rapid process, and (*d*) an allergic reaction may persist during a considerable time after the initial action of the allergen. An example of this is that of the contact-dermatitis.

Indications for operation of focal infections

In asthma patients, as well as in every other condition, chronic infections should be carefully looked for. In asthma, infections of the nose, the nasal sinuses, the tonsils and the throat are frequently present. The infections may be either the cause of asthma, or only an aggravating factor. For if during asthma the bronchi are sensitized to bacterial proteins, the inflow of infected material from the upper air-passages may provoke local reactions. Such reactions may be compared to the phenomenon of Arthus or Pirquet's reaction. Here the result will be chronic irritation, rather than the occurrence of attacks. Especially the post-nasal drip has a bad reputation in this respect.

A careful selection of cases that are to be operated on is necessary. In some cases a preliminary desensitization is preferable in order to increase the patient's immunity. If the patient suffers from nose-obstruction by nasal polyps or other reasons, suffers from a purulent sinusitis or repeated attacks of tonsillitis, he should be operated on under antibiotic and spasmolytic protection. In such cases the indications for operation are essentially the same as in patients who are not allergic.

In addition one must bear in mind that the absence of a visible focus, thus of inflamed tissue, does not by any means imply that no focus exists. To trace it is the task of the bacteriologist and to suspect it is the task of an accurate clinical observation of the patient.

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ROLE AND TREATMENT OF INFECTION OF THE UPPER RESPIRATORY TRACT IN ASTHMA*

by

J. TABART

The high incidence of rhinopharyngeal and dental infections associated with the asthmatic disease was shown off after the improvement of investigation methods (X-rays, lipiododiagnosis). Various aetiological hypotheses were suggested in this respect: is infection a cause of asthma or only a superadded cause? is infections asthma of allergic origin or not?

We confined the quotation of the works issued for the last 25 years to those dealing with rhinopathies and particularly sinusites. Our experience being scarce as regards dental infections, we cannot give any conclusive view on this subject.

I. STATISTICS

In U.S A. Cooke and Grove [1, 21] in 1933 reported 49 per cent of asthma cases provoked by various infections of the rhino-pharynx, out of a series of 688 cases. Incidence for sinusitis only was 39 per cent in asthmatics aged from 10 to 30 years, 65 per cent in asthmatics aged 30 to 50 and 83 per cent in those over 50 years. Kern and Shenk [2] out of 400 asthmatics found 70 per cent sinusitis clinically and radiologically confirmed. Kelley also [3] in 1936 valued 89 per cent of asthmatics as bearers of sinusitis in a series of 100 cases. Chobot [4, 5] out of 88 asthmatic children under 15 years age, found 67 per cent sinusitis. Reversely, Bullen [6] studying the various associated symptoms and signs in 400 bearers of sinusitis admitted to 'Rochester Hospital', valued only 25 per cent chronic non-tuberculous pulmonary affections, of which a half were asthma. As for Bivings [7] in 1940, asthmatic bronchitis is always related to an infection of the upper air passages, it was present in 35 per cent of 235 children showing upper respiratory infection.

In Europe, Haibe of Liège [8] in 1932, out of 1.000 asthmatics found: 50 per cent of cases provoked by seasonal rhinobronchitis, 25 per cent by bronchial infection, 0,5 per cent by sinusitis.

In 1940 Broerson of Copenhagen [9] holds that out of 435 asthmatics 292 are bearers of nasal anomalies. Jacquelin and Chait [10] of Paris, in 1936, out of 430 asthmatics followed up for from 4 to 6 years, found a diseased condition of the nose in 114. Valin of Mont-Dore [11] out of

* From Hôpital Bichat, Paris (Prof T. J G Turiaf)

673 asthmatics quoted 60 per cent presenting nasal lesions. In England, according to Bourne [12] asthma subsequent to nasal lesions is very common and gets much relief from surgical operation. At the Mont-Dore Congress 1950, Rebattu and Mounierkuhn, [13] reporting on the relation of asthma to the upper air passages, emphasize the high incidence of acute or chronic sinusitis, hypertrophic chronic rhinitis of infective origin ($^1/_3$ of cases) and the usual presence of rhinopathies of allergic origin ($^1/_3$ of the asthma cases). Mariano Castex, [14] then Rossier [15] quote asthmatic manifestations occuring after infection of the respiratory tract.

Quite recently Wilken Jensen [16] in 1951, in Copenhagen, finds out of 512 asthmatic children, 225 bearers of rhinopathies, of which 65 with sinusitis The same year, Kourilsky, [17] studying very carefully 28 asthmatics, could demonstrate in 20 of them the presence of microbial pathologic changes of the upper respiratory tract: bilateral maxillary sinusitis 44,4 per cent, maxillary and frontal sinusitis 27,7 per cent, unilateral maxillary sinusitis 16,6 per cent, unilateral frontal sinusitis 11,1 per cent.

II. NASO-SINUSAL ALLERGY

From the whole of such works it appears that the association of nasal and asthmatic manifestations is a matter of fact. It suggests necessarily the possibility of common reaction symptoms at the different levels of the respiratory mucous membrane Our concept of asthma is indeed one of a neuro-vasomotor rhino-tracheo-bronchopathy developing through a dual general process: an inflammatory and secretory defect of vasomotor origin and a bronchomotor defect. The ultimate phases of the process ends in obstruction of the bronchioles at the level of the lower air passages which obstruction promotes dyspnoea. In the upper tract, the oedema and hypersecretion express the different phases of the naso-sinusal allergy, which have been well described by Bourdial, Andre and Clerc. [18]

In the initial stage of acute allergy, only is oedema of the naso-sinusal mucosa clinically and radiologically detectable during the attack (in 85 per cent of cases according to the American authors) In this stage, between the attacks, the mucosa resumes entirely its previous structure.

To an aggravated stage (from repetition of the paroxysms) does correspond the serous allergic sinusitis: the distended and infiltrated mucous membrane becomes thickened; radiography confirms its permanent and non-reversible involvement Occasionally the presence of minor polypi of the middle meatus and of eosinophilia in the secreta is recognizable.

In an ultimate stage the mucosa of the sinus becomes *proliferant*, that is polypous allergic sinusitis as proven by bilaterality of the lesions, absence of purulent secreta, anosmia.

It is remarkable that the manifestations are sometimes localized on a 'story' of the respiratory tract, sometimes generalized to all respiratory mucosae from the finest bronchial ramifications up to the beginning of the nasal mucosa.

III. VARIOUS ASPECTS OF THE INFECTION IN ASTHMA

Under such conditions one may wonder to what extent such a microbial aggression as previously localized on the mucosa of the upper respiratory tract is susceptible of promoting asthmatic manifestations· in those forms where allergy and nasal infections get associated, one wonders which is the prior predominant factor.

a) *Infection, as a primary factor of asthmatic manifestations*
This is the view of Cooke [19, 20, 21] who, within a 10-year experience, could observe that in children there is in many cases a history of acute infections such as. whooping-cough, measles, pneumonia, influenza, followed after several months, by a recurrent bronchitis which finally will assume an obvious asthmatic character. Such diseases leave behind them some infection foci or some secondary 'invaders', which in their turn, become primary causes of asthmatic allergy. Until 5-year age, these foci are placed in the lymphoid tissue of the tonsils, pharynx and naso-pharynx. Following the development of paranasal sinus, the infection localizes itself fairly often in this cavities. The most commonly responsible bacteria are, according to Cooke [20] pneumococcus, hemolytic and non-hemolytic streptococcus, microcatarrhalis, streptococcus viridans

It is also the view of Kourilsky and co-workers that infection is not to be seen only in old-standing or inveterate asthma Bronchial infection occurs long before the outbreak of the initial asthmatic manifestations or is often concurrent with them. Search for the cause of *descending infection* should be systematically made at the level of the sinuses and teeth. Deep focal infection may be invisible exteriorly (sinusitis, tonsillar granuloma), surface infection may be overlooked *(purulent rhinitis, infection of the gums and interdental lingulae). Best* prophylaxis of asthma, according to Kourilsky [22] consists in removing the infective foci (operation on sinus, punctures, cleansings, antibiotics, vaccinotherapy). The *author's arguments and conclusions* [22, 23] are consistent with those previously stated by Gallup [24] Frouchtman, [25] Spoujitch, [26] Stevens. [27] Asthma takes rise from the meeting of infection and an indispensable favourable 'terrain'.

As for Jimenez-Diaz [28, 29] the part of infection inbronchial asthma is very significant in most cases (82 per cent). In a very large proportion of cases its influence may be the actual causal factor; in a lesser proportion, the infection is added to other allergenic effects, its development is encouraged by the alterations in structure and reaction of the tissues, it comes to holding a prevalent role in the activations, persistency and evolution of the asthmatic manifestations. Jimenez-Diaz considers the evolution as presenting three phases in the bronchial mucous membranes subsequently to the rhino-pharyngeal infections: 'paroxystic' phasis marked by a return to normal following each attack; 'pathergic' phasis where Forbusoni's granulomatous inflammation may be noted, reversibility of the symptoms being no longer observed; finally the ultimate 'angiodermale' phasis accompanied by deep changes: fibrinoid degeneration of the collagen system, granulomas, periarteritis nodosa nephritis or hypertension. Such an evolution is not unavoidable and may be stopped by an appropriate anti-infective treatment (antibiotics and especially microbial vaccines).

b) *Infection as a significant but non-preponderant factor of the asthmatic manifestations*

Williams and Williams of Cardiff [30] admit that infection of respiratory tract is but one of the numerous stimuli apt to establish the status of asthmatic diathesis. They noted the presence of infection in 55 per cent of asthma cases, which observation allowed them to conclude that the association infection-asthma is not casual. It seems to be one of the determining factors of the attacks but only in the proportion of 14 per cent of cases that is far less than the other stimuli: dust allergy, moulds, alimentation, emotional shock, pregnancy, menstruation, climate, fatigue. Williams and Williams do not regard the infection of the air passages as holding a preponderant part in asthma

Rackemann [31, 32] claims that the infections of the respiratory tract, either primary or secondary are significant in 'intrinsic' asthma but that one cannot decide whether they are properly a direct aggravating cause or an effect among the physical causes (depletion) and the emotional, psychosomatic causes.

c) *Infection of the upper air passages as a factor of bronchial infection superadded to allergy*

That is the opinion expressed in U.S A. by Rinkel and Randolph [33] who consider the problem of infection as negligible once the allergies from food and inhalated substances were treated. In France Jacquelin and Chait [10] observed as many improvements as negative results and aggravations in the course of treatment of 45 patients who had been operated on

from polypi, sinusites or who had experienced punctures and cauterizations: which demonstrates that there is not in all cases a causal connection between nasal infection and asthma. J. Sclafer [34] had the same opinion.

Existence of bronchial superinfection in the asthmatic children and in inveterate asthmatics under the appearance of descending infections of the upper respiratory tract is wellknown and needs no further explanation here. They constitute an episodic complication or a state of inveteracy, which from the fact of their being anterior to or associated with asthma, should not be considered a primary cause. Besides it is well-known that acute infections with high fever, of the tonsils, sinus, middle ear may induce the same remissions of asthmatic manifestations as do acute infections of the lung, for instance pneumonia. But here do intervene other 'stress' phenomena which may account for this effect.

Considering the diversity of opinions on so complex a question, one is led to assume that there is some process of interreaction between the rhino-naso-pharyngeal infections and the manifestations of asthma.

IV. POSSIBLE MODES OF ACTION OF THE INFECTION IN ASTHMA

a) *Nasal irritative 'thorn'*

This is an assumption, commonly put forward, since it was formulated by Bezançon and De Jong [35] in respect with asthmogenic pulmonary sclerosis. It has been stated that the changes in the nasal region were enough to discharge the manifestations of bronchial asthma in 'potential' asthmatics As held by Leroux [36] the notion of 'irritative nasal thorn' has been ill-interpreted. For discharging an attack of asthma a mere passive stenosis of the nose due to infection is not enough, a deep lesion of the mucosa is necessary (oedematous ethmoid and its ending in polyposis, inflammatory reactions of the same type as the underlying asthma). Rebattu and Mounierkuhn at the 11th Congress of Mont-Dore [13] together with a number of other Congressists have confirmed the difficulties in interpreting such a process. We think, for our part, that most of nasal polyposes in the asthmatic are 'witnesses' and not causative factors of asthma.

The role of the 'endobronchial microbial thorn' as maintained by focal infection of the upper respiratory tract is put forth by Haibe, [6, 38] Kourilsky, [23] Frouchtman. [25] Haibe [8] was the first to call attention to the importance of nasal and pulmonary infections in the past history of the asthmatics. They would leave a chronic infection, whose responsible organisms would irritate the ends of the corresponding nerves and would sensitize the body to their toxins on an asthma-predisposing 'terrain'. According to Haibe [37] 'the microbial nasal thorn' would be

due to staphylococcus and the 'bronchial thorn' to streptococcus. Kourilsky[23] postulates that the irritative thorn is actually and materially constituted by the endobronchial infection: infective involvement of the deep layer where the glands are situated, as well in recent as in long-standing asthma. The infection plays a determining or revivifying role. As for Frouchtman[25] the same circumscribed changes of the endobronchi (sometimes latent, therefore overlooked) maintain a condition of bronchial irritability. Descending superinfections of the rhinopharynx provoke by reflex action local or remote bronchial spasms Such infections obligatorily promote inflammatory phenomena by bacterial allergy.

b) *General microbial allergy*
Some authors suggest the possibility of a general process of microbial allergy, the allergens originating from a focus of the upper tract.

Previously held by Cooke,[20] Brown,[39] Walker,[40] Thomas,[41] Swineford,[42,43] the assumption of bacterial allergy was maintained by Jimenez-Diaz[29] and his pupils, of whom Surinyach,[44] at the last European Congress of Allergy Infection on the basis of a 'dysreactive' constitutional disposition promotes the allergic reaction of the respiratory mucosa which develops from the state of transient acute oedema to the non-reversible state of inflammation. From comparison with his own observations on 'malignant abacterial endocarditis' Jimenez-Diaz suggests that the lesion of the vessels and connective tissue is the consequence of the toxic effect of certain proteic fractions abnormal in quantity and quality as found in the plasma subsequently to the repeated aggressions of the bacterial allergens. Among English authors, Frankland,[45] Harley[46] postulate the existence of an allergy specific to the organisms of the 'focal infection'. This reaction would occur in relation to the nucleoproteins and carbohydrates, originating from the disinte-

phasis following a 'chilling'. On the one hand, the asthmatic manifestations follow in frequency and intensity a curve parallel to that of the seasonal fluctuations of bacteria in the upper tract (maximal period from September to April) On the other hand the degree of cutaneous susceptibility to the nucleoproteins of these bacteria increases and decreases in a parallel fashion. Stevens observed in those allergies by microbial sensitization a type of urticarial reactions, the threshold of which varies 1/10—10 to 1/10—4; in normal children or in those subjects with only seasonal infections the reaction is always erythematous or of a delayed type, the cuti-positivity threshold of which is always below 10—4.

c) *Acute infections of the respiratory tract as an intermediate factor to asthma*

Spoujitch[26] suggests that, in addition to cases of sensitization to microbial allergens there are cases where bacteria act as factors encouraging the allergic or microbial allergic process ('descending bronchitis opening the door to the penetration of exogenous allergens'). Out of the infection periods, the same subjects exposed to the same allergens do not feel any asthmatic disturbance; when they were cured from their infection, the asthma does not recur. Other authors (Harley)[46] admitted that a focal infection may lower the threshold of the respiratory mucosa to the allergens brought in by the blood stream (bacterial) or by allergic load (Duchaine).[65]

d) *Infections of the upper tract as intrinsic factors of asthma*

Chobot,[4, 5] Bivings,[7] Stevens[27] pointed out in children the frequency of asthma manifestations, just concurrent with chillings, by acute bronchio-alveolitis leaving or not leaving residua for secondary re-infections There is in this stage no properly called microbial sensitization and only does the irritability of the mucosa from the infection determine the obstructive inflammation of the bronchi. In a more advanced stage the repetition of the infections subsequent to the predisposition to allergy or in the presence of the 'debility of the mucosae", as pointed out by Flurin,[47] Sergent[48] produce a certain degree of chronicity in the asthmatic manifestations As claimed by Salen[49, 50] one deals with a vicious circle: allergy predisposing to infection, infection predisposing to allergic manifestations. As for Williams and Williams,[30] inflammation does not exert only a determining action on asthma, it predisposes to the various specific or non-specific stimuli such as wind, fog, vapour, changes in temperature.

In fact the question presents great complexity, whichever the pathogenesis adopted; the main argument as often evoked is that the removal of the infectious foci of the upper tract and of their remote effects is followed by betterment in the asthma condition

Our personal opinion is that the slight or obvious involvement of the [illegible]

express the presence of oedema and increased serous secretion, an expression of allergic disease of the whole mucosa. Sinusal infection and its descending extension is a trivial process induced by retention of the secretions due to the swelling of the mucosa in the cavities. One may say that the 'trivial' infection is an additional phenomenon. It is not a cause of the properly called asthma, for, in spite of operations such as punc-

tures, drainage, the asthmatic manifestations do persist, as do recur the rhinopharyngeal manifestations after a more or less long time....

It is likely that the acute or dragging infection helps in the discharge as suggested by Spoutich [26] and Harley, [48] or by weakening the immunologic defences of the system, or by allergic load (although the question of specific microbial allergy is still difficult to demonstrate clinically).

It is certain that repeated and chronic infections with descending tendency encourage the organization of 'ectasiant' and 'stenosant' disorders, so common in asthmatics. [53, 54] Thus is any rhino-microbial aggression a threat of aggravation and exacerbation of pre-existent chronic infection.

VI. TREATMENT OF RHINO-PHARYNGEAL INFECTIONS IN ASTHMA

We think that therapeutically any dragging infection of the rhinopharynx should be treated with active but non-irritant medications, free from secondary allergic or vaso-motor reactions.

Against nasal obstruction (due to minor infection or association of infection and allergy) we advise 'minimal' focal cares. We disapprove of the use of galvanocautery or silver nitrate cauterisations, applications or pulverizations of anesthetic or vaso-constrictive mixtures such as Bonain's mixture, mixture of aromatic sympathomimetic oils. We only advocate spaced nasal instillations of antihistaminics (preferably fluid vehicles or neutral excipients of Carbowax, vaseline, glycerin type). Instillations, pulverizations or sub-mucosal infiltrations of hydrocortisone acetate are advisable in the cases of full impermeability of the nasal ventilation. Their efficiency is dramatic but transitory. Usual cares in most cases ameliorate those conditions maintaining the retention of the secretions in the closed cavities. By setting up the drainage of the catarrh one causes the infection to clear up by itself.

In the stage of acute or subacute rhino-pharyngeal infection, the use of antibiotics locally or systemically is indicated. The choice of the antibiotic should be guided most often by the previous test of susceptibility of the organisms from the rhino-pharyngeal secretions to the different antibiotics We make reserve as regards penicillin, owing to its high allergisant potency. Better and durable results may be expected from sulphamides, but these are more easily tolerated by systemic route than by local route.

In the cases of purulent sinusitis we prefer medical management: decongestive inhalations of menthol alcohol at 4 per cent, antibiotics aerosols (penicillin excluded), repeated punctures, cleansings of the maxillary and ethmoidal sinuses by Proetz's method.

Dilapidating surgical interventions (exposure of the maxillary sinus

with drainage by nasal counteropening, curettage of the ethmoid) should be dissuaded in most cases of sinusitis in asthmatics. Relapses after a certain length of time are not infrequent. Tendency of the asthmatic èvolution towards aggravation is more often the rule than generally believed. We also disapprove of the other endo-nasal surgical interventions: resection of septum, luxation and exeresis of turbinate, etc. Removal of polypi is only indicated in the case of big polypi causing a permanent defect to nasal aeration.

Vaccinotherapy with stock-vaccine or autovaccine from germs collected from the sinuses or post-nasal spaces, injected by intradermic or subcutaneous route has effected unquestionable sedations. Prophylactic vaccination, out of the infection periods, should be performed with very low doses from 1000 to 100.000 germs per cc. because of the hypersusceptibility of the patients to the bacteria utilized We had the opportunity of using autovaccines during infection periods. Under these conditions the dosage had to be far more reduced still the scheme of utilization being similar to the methods of specific desensitization called 'coseasonal'.

Specific desensitizaton against dusts and moulds, by neutralizing the chronic factors of oedema of the rhinopharyngeal mucosa has yielded gratifying results which may be compared with those obtained by Hansel. [51, 52]

Lastly the thermal sulfurous cures against the infection: Luchon, Cauterets, Allevard; the cures against the asthmatic terrain: Mont-Dore, La Bourboule, Saint-Honoré, are prophylactically very beneficial against infections of the air passages in asthmatics, especially with the use of thermal gas.

Conclusions

1) Infection of the upper respiratory tract in asthmatic diseases is a very frequent phenomenon, but its being anterior in time does not mean necessarily that its role is preeminent.

2) The infection easily develops owing to the fragility caused by an increasing irritability of the whole respiratory mucosa of the asthmatic.

3) The infection is occasionally a determining factor, but usually an aggravating factor.

4) It is essential to treat the nasal and sinusal infections. Medical management is preferable to surgical procedures which are traumatisant and may be an aggravating factor of the asthmatic disease.

5) Specific treatment of the microbial allergy has not yet given conclusive results in the asthmatic disease.

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occasions in the case of intrabronchial foreign bodies and benign and malignant tumours of the trachea.

b) It is true that in this group a clear clinical picture of bronchial asthma is observed, but further bronchological examination shows anatomic anomalies of the bronchial tree. In this case we usually find anomalies in the form of a bronchial cyst or bronchiectases, etc.

It is still quite uncertain whether the bronchial asthma is caused by these anomalies, or whether the two diseases result from a particular constitution. We hold the view that in cases where anatomic anomalies are found, an attempt should be made to cure these anatomic anomalies. Such diseases constitute a constant source of danger on account of recurring infection, haemoptyses, etc. We observed several cases of bronchial asthma in conjunction with serious infection of the bronchial mucous membrane. After treating this infection we usually saw a marked improvement of the bronchial asthma. This is quite the opposite of the assumption that an infection would produce stress reaction, thereby reducing or removing the bronchospasm We observed in a number of cases that surgical treatment of bronchiectases or bronchial cysts led to a marked improvement or cure of bronchial asthma.

SUMMARY

1) It is essential that every patient suffering from the serious syndrome of bronchial asthma should be subjected to a complete examination. A complete examination of bronchial asthma should also include bronchological examination as an important feature, in addition to a clinical and allergic examination. Lung-function examination is also very important.

2) Pseudo-asthmatic conditions are frequently observed in bronchial diseases in conjunction with bronchostenosis.

3) The clinical picture of bronchial asthma is observed in conjunction with chronic bronchial infection on the bottom of bronchiectases or bronchial cysts. In this case resection therapy can sometimes give excellent results, not only as regards the removal of the infection, but also the disappearance of bronchial asthma.

DISCUSSION

R. ALEMANY-VALL

Though the surgical treatment of asthma is empiric, we think that we should not disregard it, because with this we can obtain a disappearance of the crises for a rather long time

We want to speak here of the extirpation of the second and third pair of dorsal ganglia, or the resection of all the nerves of the plexus hiliarus, except the 'trunk of the pneumogastricus' and of the 'recurrents' With the first operation done by Prof Piulachs we have obtained some good lasting results, for more than a year, with an inveterate asthmatic, whose case we could not get improved by any means The second operation (resection of the nerves of the flexus hiliarus, at first unilateral, later on bilateral) was done by Dr. Margarit, a thorax surgeon.

This operation has enabled us to see easily all the organs of the area, because they were surrounded by very few adipose tissue

These operations are delicate, particularly those which are concerned with the anaesthesia

This anaesthesia must be perfect, executed with the most modern instruments, because the bronchial contraction only ceases with great difficulty. These patients are only bronchial asthma patients, without other lesions (bronchiectasis, carcinoma, tuberculosis etc)

THERAPY OF EMPHYSEMA

An Abstract

by

N. G. M. ORIE

It is very difficult to give any summarizing article on therapy, because [illegible] in therapy is the details of its application and the details of the [illegible] chanism is not understood.

The fact that the treatment of emphysema has been included in this symposium on asthma indicates that both diseases are considered more or less identical.

I am inclined to agree with that point of view. It implies that obstructive emphysema is a result of bronchial obstruction which is in the majority of cases of asthmatic origin. I would even go further and suggest that most of the other lung diseases in themselves are unable to produce emphysema.

That means that if emphysema is met with, e.g. in tuberculosis, in sarcoidosis or in bronchiogenic carcinoma, it is not related to that disease but it is the result of an independent asthma existing simultaneously with the tuberculosis, sarcoidosis or carcinoma. [1]

This can only be proven by family history and by allergic phenomena existing with certainty before the disease in question.

Witkop has given some very clear data on sarcoidosis.

We have some similar observations in tuberculosis (De Vries).

Distension of the lung does not give the functional pattern of emphysema.

If the foregoing is true, every case of emphysema will show:

a) a certain degree of asthma

b) a certain degree of irreversible anatomical change, being the effect of the asthma.

We do not know the exact relations between the two components. Sometimes next to these two features, which are always present.

c) a complicating infection and in those cases we are often dealing with overburdening of the right heart, cor pulmonale:

[1] We have stressed elsewhere that the situation is different in so-called idiopathic bronchiectasis when we consider the asthma as a causative factor.
It cannot be excluded that a simultaneously existing asthma alters the course of the disease in the other groups.
In using the term asthma we use it in the broad sense: allergic (?) expiratory embarrassment on a constitutional base; often without clearcut attacks (see Israëls).

All this means that there is a fluid transition between asthma and emphysema. Most of all in older age groups where the anatomical effects as a rule are more pronounced.

As a matter of fact there is no sharp distinction between old-age asthma and emphysema, although there are cases in which the asthmatic factor or the anatomical pathology is but little pronounced.

Therapy

Which are the therapeutic possibilities of emphysema?

Unless we know the cause of asthma, we have no etiological therapy. The conclusion from the foregoing is clearly that to a large extent the therapy of emphysema goes together with the therapy of old age asthma, but even the problem of the therapy of old age asthma would be too extensive to treat in a few pages.

We therefore will give only a few summarizing remarks mainly in relation to our own experiences.

Symptomatic treatment

Treatment of complications

A) Infection (which is present in only a minority of the cases; although patients with emphysema show a strongly marked tendency towards bronchial infection).

We have not to go into details on the antibiotic therapy of infections which would be far beyond the scope of this paper. We can only point out that in the chronic infections Haemophilus influenzae usually is the infecting agent whereas in acute infections usually pneumococci are found. Adequate antibiotic treatment follows from the etiologic agent and from the sensitivity of that agent towards the antibiotics.

It must be mentioned however that in chronic cases most of all in this older age-group the danger of increase of asthmatic symptoms after a successful antibiotic therapy is far from imaginary.

Severe, even fatal exacerbation of asthma after successful antibiotic therapy occurs only occasionally, usually the beneficial local effects of the therapy are predominent.

The possibility of the incidence of severe reactions is no reason to omit antibiotic therapy, but it may be a reason for follow up with ACTH therapy if the asthma is more predominant after the treatment.

B) Right heart failure—oxygen therapy

A second complication which may need therapy is a burdening of the right heart or straightforward right heart failure.

In uncomplicated emphysema (unless in terminal stages) there is no

marked hypoxia and therefore there is no burdening of the right heart to a considerable degree.

Severe hypoxia in emphysema means: infection in 99 out of 100 cases. Once in a while a severe asthmatic attack or severe diffusion disturbance has the same effect.

In that case hypoxia calls for oxygen therapy and at the same time right heart failure is impending.

In infected cases of emphysema with burdening of the lesser circulation this type of therapy is necessary.

It includes: *antibiotic therapy* as a most important measure and next symptomatically cardiac stimulant drugs.
bronchodilators
O_2

The latter however may be a dangerous medication in depressing the ventilation. It has to be applied with the utmost care and sometimes additional measures (stimulation of the central nervous system or artificial respiration) are necessary.

Treatment regarding the anatomical change

Pneumoperitoneum

Literature on this subject is confused.

Improvement of diaphragma movement is frequently seen but not apparent from function tests.

One may visualize that the improvement of the diaphragmatic movement is counterbalanced by the unfavourable influence on the cheque-valve mechanism, which increases its effects when the lung is brought from strongly inspiratory into an expiratory position.

Our own experience is disappointing with once in a while a successful case. Barach states that in good cases the venous pressure falls on induction of pneumoperitoneum.

Maybe the choice of patients will be easier if the methods of measuring the elastic and viscous properties of the lung are simplified.

Our actual experience with these methods is too limited to draw any definite conclusion

Therapy of the asthmatic factor itself

Anti-allergic therapy

Positive skin- and inhalation-tests are much less frequently seen in this (older age) type asthma then in the younger groups. We therefore think that specific desensitization less often takes part in emphysema therapy than it does in younger individuals.

Symptomatic drug therapy

Because this has been discussed by the other lecturers I think I may only mention the points of interest for the emphysematous patients.

Generally speaking the drug therapy does not differ significantly from that in asthma in general.

There are however a few exceptions

Atropine-like substances in our experience give better results in the older age groups (with less allergy?) than in the young patients (with pronounced allergy).

Anticholinergic antihistaminics act very favourably in both groups. The mode of action of aminophylline is neither understood in young nor in older age-groups.

ACTH—Cortisone

Our therapeutic results demonstrate that ACTH (and Cortisone?) is much more effective in older people than in young ones.

This is in accordance with the fact that strong allergic reactions cannot be handled with ACTH and on the other hand that this type of allergy is uncommon in the older patients Dr. Ten Cate has given you a number of examples of the results of ACTH in younger and older patients.

If we accept that the development of asthma and emphysema in older people is largely dependant on disturbances of normal pituitary adrenal reactions (which is hypothetical) we can much more easily understand the good results of ACTH particularly in this group and at the same time we can easier accept the fact that as a rule this therapy has to be continued once we have started it.

Fever therapy

S oil—typhoid vaccin.

This implies that this type of ACTH substitute therapy is effective once in a while and at the same time that these results are seldom lasting.

Some protracted effect is met with however in a number of cases (because here the lack of autogenous Cortisone is not substituted but the endogenous production is—temporarely—stimulated?)

SUMMARY

Summarizing I may say that from a practical point of view antibiotic therapy is sometimes useful if an infection is present It has however to be kept in mind that particularly in this group the elimination of the stress due to the infection may be very harmful and even fatal.

Desensitization is not often used in treatment of emphysema. Maybe in these cases parts of its result are aspecific (baterial vaccines).

Pneumoperitoneum has been disappointing but offers successful treatment once in a while.

Symptomatic drugs are useful, anticholinergic substances and anticholinergic antihistamines have provided useful additional help, most of all in the older group. Their effect in the protection test is clearcut.

ACTH has its best indication in this group of older people. It has to be continued however in an effective dose.

Stimulation of the pituitary-adrenal system therefore offers not seldom temporary benefit.

Psychotherapy: We have insufficient data in this type of treatment. I could not help introducing a certain amount of a speculation and conjecture in this paper.

I apologize—and I am fully aware of the necessity of doing so—but I may add that the approach to therapy of any type of asthma is hardly possible from a purely factual point of view.

I sincerely do hope that this situation will change as soon as possible and that our efforts may contribute to the realization of this area of asthmatherapy.

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A few papers in which data are given concerning *our own* experiences in this field, are:

Asthma bronchiale, etterige (bacteriële) bronchitis en het endocrine systeem (Bronchial asthma purulent (bacterial) bronchitus and the endocrine system) Thesis A. A. ISRAËLS, Groningen 1952

Longfuncties na longresectie (Lungfunctions after lungresection) Thesis E. E. M. GEELEN, Groningen 1953

Onderzoek bij asthmapatiënten naar overgevoeligheid voor verstoven allergeenextracten (Investigation in asthmatic patients of hypersensitivity for aerosolized allergenic extracts. Thesis H J. TEN CATE, Groningen 1954.

Thesis H. J SLUITER, in press

Relation entre bronchiectasie et allergie, by N. G. M. ORIE, E. HUIZINGA, A A. ISRAËLS, E E. M. GEELEN, H J. SLUITER and R. WARRINGA. in. *Les Bronches, vol. V,* 1955, No. 2.

Resection in bronchiectasis, in press.

Le rôle de la tuberculose et des infections non tuberculeuses dans le développement de l'insuffisance cardiaque droite, by N G M. ORIE, F S. P VAN BUCHEM, H. J. SLUITER and A. J F. DE VRIES. in: *Acta Cardiologica, T IX,* 1954, No. 4.

DISCUSSION

TREATMENT OF EMPHYSEMA

by

BOEN SWINNY

The treatment of emphysema falls into five parts:

1) *Study of the patient.* 20 per cent of moderate and advanced emphysemas will

under study. In addition to this study, the patient deserves to have careful repeated studies made of sputum for infection, both by plating and by culture. Radiography and vital capacity studies should be done. Vital capacity should be done both before and after the use of bronchodilator, such as isuprel, as often this

watery as possible in order to wash out plugs and tenacious secretion by the use of expectorants. Iodides, especially potassium iodide, orally or in combination with broncho-dilators serve this purpose.

b) Keeping the bronchial secretion free of infection by use of vaccines, antibiotics, oral, parenteral or by aerosols; the latter are to be preferred as there is the additional value of being able to combine the liquefying agents, such as Alevaire with a bronchodilator such as isuprel

3) *Drug therapy.* Bronchodilators, such as ephedrine orally, or the use of hand sprays containing epinephrine or isuprel. Decrease in excess body fluids by Diamox

experience, will not tolerate emphysema belts

5) *General health* Reduce excessive weight to normal or slightly below normal Usually prohibiting smoking is helpful. Watch out for anemia because the patient that has the normal blood count breathes easier than the one who has a decreased red count and hemoglobin. Focal infections should be cleared up. A well balanced diet with a light evening meal often helps the patient rest better at night.

A CRITICAL REVIEW OF THE STATISTICS OF ASTHMA-THERAPY

by

A. HEYMER

The theme of this very interesting meeting is. the therapy of asthma bronchiale. The possibilities of the treatment of this illness have been dealt with thoroughly by the individual speakers in the course of this meeting. They began with a view of the patho-physiology of the asthmatic attack, and continued with the specific and non-specific desensitization, the vaccine-therapy, diet, psycho-therapy, the physical and hormonal treatment, and also the anti-infectious therapy. The gentleman speaking before me has given a critical view of these kinds of asthma-therapy.

Now there remains the task for me, being the last speaker, to give a critical report of the statistics of the success of asthma-therapy. There will be not enough time to speak of individual publications, not even to discuss groups of individual kinds of treatments. Also I would most likely trouble you too much with this now at the close of this meeting Therefore I shall take pains to deal with some points which are important for the evaluation of the successful treatment of asthma. I think these *points are important for the development of asthma-therapy in general.* I shall base my argument mainly on the teaching about the methods of the therapeutic-clinical research of my highly esteemed teacher Paul Martini.

For the evaluation of the success of asthma-therapy the same rules have to hold, basically, as for all other diseases. However we must admit that there exist especially great difficulties in the case of asthma bronchiale. Up till recently the clinical picture of asthma bronchiale was not a very uniform one. I should like to omit the psychogenic asthma in the following exposition and I should like to centre on the purely allergic-asthma. I admit that in all most every clinical picture of asthma there are psychogenic factors and I include the case in which e.g the limit of tolerance towards allergens has been lowered through a psychial trauma so much that a genuine allergic asthma originates. If one wants to evaluate the therapeutical success of such a clinical picture in which many factors, partly of immense number, play a role, one often is confronted with insurmountable difficulties. One has to exclude those cases of sickness in which asthma is merely a concomitant symptom as it may be the case in bronchiectasis, silicosis, Boeck's sarcoid,

emphysema together with chronic bronchitis et al. In the following exposition only the true asthma bronchiale, caused by allergy, is meant This clinical picture, too, is various. In one case it appears in the form of severest attacks, in other cases of dyspnoea, which never quite disappears, continues in between the individual attacks. Then there are other clinical pictures in which a dry bronchitis continues to exist From this one will understand that the therapeutic possibilities of influence, too, are different in each case. An evaluation becomes more difficult yet if other diseases are present simultaneously, or if irreversible subsequent phenomena have appeared, e g emphysema or an injury of the right heart. Martini had to admit that it is hardly possible to test a '*collective group of asthma patients*' according to the principal of therapeutical comparison. The *individual patient*, therefore, needs to be observed very closely during the course of his disease, in which individual periods of his disease are to be compared. If the patient is willing to stay hospitalized over a sufficiently long period of time, there is the possibility to have a preliminary period of observation, a therapeutical observation and a final observation. The test is of higher value if there is the possibility to conduct several periods of observation and to compare these. The result of this study still increases in value if one succeeds in carrying through a 'reversible test' with a medicament, i.e. after giving the medicine the symptoms of asthma disappear, they reappear after the discontinuation of the remedy and remain during the giving of a pseudo-remedy, they disappear again at the renewed giving of the genuine remedy although the patient is unaware of this.

Which signs does asthma bronchiale have that point to a therapeutical influence? They are rather numerous. Subjective statements may be of importance. There is the danger, of course, that psychogenic influence play a part in this The most impressive sign is the asthmatic-attack. Its characteristics are its severeness, its repeated appearance and its more or less long intervals without trouble and symptoms. There exists a possibility of evaluating the asthmatic attack objectively in regard to its patho-physiological results, which shall be dealt with below. Clinical factors which point to asthma bronchiale and its capability of being influenced therapeutically, are the physical state of the lungs with dry bronchitis, with phrenoptosis, the position of inspiration of the thorax; the measurable limitation of the respiratory movement, of the eosinophilia in blood and sputum, the amount of sputum, and its content of mucus, of Charcot-Leyden's crystals and of Curschmann's spirals, and with the forms of asthma caused by infection of the bacterial flora of the sputum, its influence upon the circulation, and in severe cases of cyanosis, also. Martini thinks that the most important signs of asthma bronchiale and of its severity are the kind of attack and its

frequency. The requirement for a systematic test of remedies of an asthma patient is an exact, continuous registration of symptoms. O. Kuhne and H Martini have drawn up a scheme which they call 'asthma clock' (Fig. 1).

One can easily see that such a registration provides us with information about the remedies which would be useful in each individual case. We have to add, however, that most of these medicaments act only symptomatically, i.e they remove or diminish those appearances which bring the cause of the disease to a head. These individual observations provide no basis for conclusions as to asthma patients in general. For this we need a tabulation of a large number of sick people, which is subdivided into respective groups, and of which we can see the efficiency of such a remedy. The larger the number of patients who are therapeutically influenced, the higher we can evaluate the therapeutical effect of this remedy. One must not overlook the fact that asthma bronchiale is the result of complex processes. The clinical picture which we find in the asthmatic attack, is usually the result of allergic reactions, which have developed over a long period of time up to this climax. If the asthmatic attacks have occurred for years already, changes in the anatomical substrate have mostly taken place, changes which cannot be expected to be influenced by ordinary remedies for asthma. From this we see, however, how difficult the evaluation of a therapeutic success of a remedy can be. Hansen pointed out that one may not expect very much of a remedy for asthma, that a final success can only be effected through a study of the causes. Only this gives reason to expect a healing or preventing of asthma bronchiale.

As was said above, formerly we had to rely mostly upon the usual clinical symptoms in evaluating the success of the treatment of asthma bronchiale. The study of the patho-physiological change of respiration of the asthma patient have now given us several possibilities by means of which the results of a remedy upon the respiration can be checked more closely and more objectively. A rough approximate estimate already permits a measuring of the apnoea and of the vital capacity. More informative is a study with the aid of pneumotachygraphy. We have tested our patients now for about 20 years by means of Fleisch's pneumotachygraph. It permits to find out the respiration typical of asthmatic patients, and also it shows any change during the therapeutic influence of a medicament, as the following graph indicates (Fig. 2).

We would think a 'normalization' of the asthmatic patient to be due to a remedy, if it comes to a chance of frequency, of the minute volume, of the time of exhalation, of the maximum velocity, and also of the proportion of medium to maximum velocity. That can be seen in the graph.

Hour: 12 14 16 18 20 22 24 2 4 6 8 10 12

Day	Mark	
1	25,4	1st-16th day observation in advance
2	54,0	
3	37,5	
4	18,0	
5	12,2	
6	6,8	
7	19,0	
8-13	6 days general improvement	
14	12,2	
15	3,1	
16	3,1	
17	1,8	treatment with placebo
18	1,0	
19	4,5	19th-25th day Therapeutical observation with Taumasthmon Caps
20	0,6	
21	0	
22	0	
23	2 5	
24	2 5	
25	0	
26	2 5	
27	1 5	

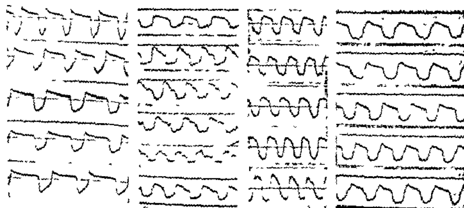
■ Heavy asthma attacks non reacting at any therapy (inhalation or by mouth with Asthmolyt)

▥ Moderate to high attacks reacting at a therapy with Asthmolycitis by inhalation or by mouth

▤ Light wheezing, therapy unnecessary

Fig 1

In the above scheme are registered the severe attacks, the medium to slight attacks and merely troubled breathing They are registered for each day by hours Over a period of 27 days the appearance of the patient has been taken down in the time of preliminary observation, during the pseudo-treatment and during the therapy



Knipping's apparatus, in its modern form, cannot be used in the case of an attack. But often it can be used in an interval between attacks. It provides us with excellent clues for the figures of the outer and inner respiration. Further methods for the test of the function of the lungs, especially in the case of an asthma-patient, have been dealt with in a monograph by Wyss. They cover respiratory mechanics, alveolar ventilation and the blood circulation in the lungs The complementary air, respiratory volume, supplemental air and residual air, as well as the functional residual air during maximum ventilation is of importance. For 2 years we have very successfully used Wyss' and Hadorn's pneumometer in our clinic. The apparatus is handy, easy to operate, and in repeated applications yields results which can easily be compared, and which change in proportion to the betterment of the asthmatic condition. It ought to be used today in asthma research. The asthma patient shows a great decrease of the results of the pneumometer during the attack, a slighter decrease in the latent condition. The results constantly change during recovery because of therapeutic influence Similarly one can use the Tiffeneau-test to determine the severity of an asthma case. However, the pneumometer is used in this case. Wyss indicated methods as to the determining of the resistance of current in the bronchial system. He also tried to use these in the evaluation of the severity of an asthma case

During the last years the possibility to get statistics of the success in asthma treatment with new means, has become considerably better. I regret to say that they have not been used accordingly by the authors who have dealt with this problem In many publications only general impressions are reported without stating this reason and what kind of therapeutical test had been used The number of those publications which survive criticism and from which truly convincing therapeutical conclusions may be drawn, is very small. For obvious reasons I cannot go into details about this The methods of therapeutical investigation are incomplete in many cases This is the reason for preventing us to hear with final certainty about many remedies in regard of their therapeutic effect, although they are used daily on thousands of patients. What do we know for instance about the success of the treatment with antihistamines. Daily we read that their application promises assured success in the case of an asthmatic attack, while a number of excellent researchers (Friebe et al.) doubt any effect at all. It would be a rewarding task to find out whether and how much we help the patient with antihistamines.

Wyss rightly warns us to use new 'asthma remedies' uncritically. He demands they should be examined by way of an exact test of the function of the lungs. He tested and compared aleudrin, solophyline and physio-

logical salt solution in aerosol form. He found that water or physiological salt solution have almost the same good effect as soluphyline which had been recommended highly until then in the form of aerosol. Although many authors already had proved in a number of tests, that theophyllin in the form of aerosol is ineffective, it is recommended again and again.

Recently a renowned author maintained during a discussion that he could heal 95 per cent of asthma patients through psychotherapy. I was surprised at this therapeutical optimism But I began to understand it a little when I realized that this statement was not supported by convincing therapeutical investigations. According to Martini, however, these should be demanded for the 'psychosomatic' medicine and also for the psychotherapy of asthma bronchiale

THE RELATION BETWEEN THE POLLEN FOUND IN THE SURROUNDINGS OF THE PATIENTS AND HIS ASTHMATIC CRISES

by

R. ALEMANY-VALL

During thirteen months we examined the pollen found daily (24 h) in the air of Barcelona, collected in the Durham apparatus exposed on the terrace of the Municipal Hospital of Nra Sra. de la Esperanza where the allergy-service is established. We have analysed a pollen coloured with fushina solution and examined it in its smallest details, after being fully familiar with the pollen collected direct from a hundred different botanical species. We have also studied meteorologic conditions having influence on the deposit of pollen, together with local and regional botanical data; morning rains clogged this deposit; the afternoon and evening rains had a much lower effect in this respect. Relative atmospheric humidity was the lowest between 11 a.m and 2 p.m —these were the hours where the largest quantities of pollen were dispersed; here was a much larger number of pollens considered allergenic in March, April and May, months in which athmospheric humidity remained persistently the lowest.

This preliminary study helped us to know the microclimate of pollinosis patients (24 h. or 8 a.m. up to 4 p m. or 4 p.m. up to 10 p.m. or 9 h. next day).

Thus, we succeeded in finding at times, by means of the Durham apparatus, the pollen responsable for the condition: such as the *Chenopodium* (about 28 elements) from 8 a.m up to 4 p m., on a four square centimeter surface of exposed slide; the pollen of *Tilia argentea*, abundant on the slides, and proceeding from neighbouring plants on days when some patients had asthmatic crises; the pollen of *Phitolaca dioica* in summer and at the beginning of autumn; the pollen of *Parietaria officinalis*, from 400 elements up to 10 in four square centimeters of slide, exposed near the plants where the patients lived, and according to their blooming times. Far from these surroundings, in town, far from these plants, the urticaceous plants did not reach a pollenproduction of 10 grains per 4 sq. cm. in May. The gramineous plants had up to 20 pollens per 4 sq. cm. in Barcelona, even in the central parts of the city in which no gramineous plants seemed to exist, where, however, we have found *Poa annua* and *Millium multiflorum*.

The pollen of *Platanus orientalis* found by us from 100 grains to 2000

grains per 4 sq. cm. (Montserrat) according to surroundings less abundant or abundant with these plants.

We have seen that there was a certain relation between crises and the quantity of pollen; the crises occurred near the places where these plants were plentiful except, perhaps, the gramineous.

Barcelona has, perhaps on account of its general geographic conditions, protection against winds, relatively high temperature and highly varying humidity; more pollens and spores of fungi on the exposed slides than places farther away from Barcelona, having an open field, more frequent winds of greater intensity and larger number of plants none of which are frequently found in Barcelona.

We have intended to establish a classification of the spores found on the slides according to their sizes, forms and colours even if such classification would forcibly remain imperfect of the origin of the spores. We think that such an orientation would be sufficient for the physician:

1) The Ascomiceti. 2) The Macròsporium type. 3) The Alternaria type 4) The Uredosporas. 5) The Teleutospores. 6) The Hemilthosporium, Sincephalastrum, Spondylcladium. 7) Hormodendrum and Cladosporium 8) Large non classifiable spores. 9) Small non-classifiable spores.

Round the end of spring, summer and autumn there was a much larger quantity of spores than in winter; there were many days, when we found 30, 40 and more spores, and on the other hand, relatively few pollens.

SPECIFIC TREATMENT OF ASTHMA

by

R. ALEMANY-VALL

The treatment by pollen is quite efficient at the early stages of the pathologic condition; these stages are counted by seasonal years when only conjunctivitis or rhinitis are present. Later when asthma appears,—also of pollinic origin, although the whole picture may disappear specially in those sensitive to gramineous plants; in those who are sensitive to other pollens, a more or less seasonally evident rhinitis may remain present, in spite of a specific treatment.

In Barcelona we have patients sensitive to gramineous plants, whose symptoms disappear even in the course of the same season, if they are then subjected to the treatment, but do not appear during the season if the preseasonal treatment has been followed.

Patients sensitive to platanes suffer from rhinitis and asthma, improve by the treatment, although, generally, not quite so much as is the case with those sensitive to gramineous plants; this occurs also in those sensitive to 'Parietaria officinalis', of which many cases may be seen on the Mediterranea Coast, this depends on the larger diffusion of pollen in the local ambient air of the patient, in proportion to neighbouring plants When there is a large quantity of pollen present, the treatment may even give less effects.

We administer injections on alternate days, or one every week or two weeks from one tenth to ten parts of 100–10,000 units for c c. This specificity is the clearest and most evident of all allergic affections. Cutaneous reactions remain positive even out of season—these reactions to certain pollens will reoccur even years afterward in patients without any crisis or very slightly affected (Parietaria) Those sensitive to chenopodium album respond very well to the treatment. We found this pollen not only at the beginning of autumn but also in summer, spring and even in winter.

We have not seen pollinosis crises only appearing during the night; we have seen, however, night-crises in patients suffering from daily crises; we have hardly seen any pollen in the houses of the patients, and found a little at night on the slides.

We saw cases sensitive to the pollens of Cosmos, Aster, Gladiolos, Daisies, etc. in florists, showing large cutaneous reactions and even focal reactions by simple scarification, with pollen above them. We do not advise a desensitizing treatment for these patients living in

contact with these plants and whose crises begin already in June.

Those sensitive to both pollen and dust when the latter is widespread in the ambient air of the patient, but only in months of intensive pollen-formation, specially in Parietaria (April, May or May-June) must be treated only with pollen, not with dust; when these two months have passed, the dust does not act any more, although pollinosis crises may occur, less intensively, on account of there being less pollen.

We have not often seen patients sensitive to hairs; these always improve under treatment, provided that the ambient air is not too full of hairs In our service of allergy in the Medical School, the separation of various flour-proteins was obtained (proteose, globuline, gliadine and wheat glutenine; also albumin and rye-globuline) which have been administered as diagnostic and therapeutic means for asthmatic bakers; we have even obtained pseudopodic reactions in them, in general, proteose and globuline were those substances which reacted most, but the therapeutic results were relatively poor.

THE USE OF GOLD SALTS IN BRONCHIAL ASTHMA*

by

LINO BUSINCO

A considerable number of serious difficulties prevent the formation of a clear pathogenic picture of bronchial asthma. This illness, which at first was interpreted as a simple manifestation of hypersensitivity in the bronchial area, now appears to be dominated by a group of factors, not all of which have been evaluated with any degree of precision. Among those elements which accompany the simple allergic situation, we must take into consideration the nervous dystonia, the diathesis, the circulatory disorder in the pulmonary area etc. At times these pathogenic factors sum up with varying intensity, one in regard to another, or they interfere, creating a mutating pathogenic background to the usual clinical manifestations of the asthmatic dyspnoea. This uncertain situation engenders, in practice, the difficulty of controlling bronchial asthma with efficacious and decisive therapies.

For several years, among other medicines for the treatment of bronchial asthma, we have been using a composition of gold salts (gold tribromide and tetra-bromide) associated with iodine, arsenic and quinine (AM 49) Administered orally, this compound has constantly given a good percentage of favourable results Out of 80 patients treated up until the present time, we can show cures or notable improvements in 60 per cent, slight improvement in 20 per cent and 20 per cent of failures The therapy is tolerated without difficulty and frequently has given surprising results even in severe cases, Rascher, Rieder, Froesch, Oehl, Steinbacher, Kleinsorge and other authors have reported similar results. The favourable activity of gold salts on bronchial asthma has also been observed by Dudan, Brunel, Cans, Jacquelin, etc It is likely that this depends, at least in part, on an activity of the gold salts on the histiocytes operating as genetic antibodies. As well as being located in the germinating centres of the lymphoid organs, these histiocytes are also to be found near the walls of the capillaries so that they are readily accessible to the gold salts. In support of this interpretation is the fact that, during therapy with gold salts, we have been able to observe, contemporaneously with the clinical improvement, a decrease in the rate of the gamma globulins which are known to be vectors of antibodies. This decrease may very probably be attributed to a lessened genetic activity on the part of the histiocytes damaged or disturbed by the gold salts. When the proportion of antibodies is either absent or reduced, the hyperergic reaction would thus be eliminated or at least mitigated.

* Institute of Medical Semeiology of the University of Rome.

THE FREQUENCY OF BRONCHIAL INFECTION IN ASTHMA AND DESCRIPTION OF A METHOD FOR STERILE REMOVAL OF BRONCHIAL SECRETION*

by

HELGE COLLDAHL

When bronchial secretion is drawn up through a bronchoscope, contamination with throat bacteria often occurs.

If bronchial secretion was collected by introducing a sterile catheter through a tracheal tube after intravenous narcosis with Evipan and Scoline no contamination occurred in 90 per cent of examined cases.

With the last mentioned investigational technic it could be shown that asthmatic patients, when BSR is not elevated, do not have bronchial infection oftener than patients with healthy lungs.

Further it could be shown that patients with 'mucopurulent' sputum often have no bronchial infection The appearance of sputum, which in these cases is often rich in eosinofilic leucocytes, is due in all probability to the allergic reaction in the bronchi.

In the investigated material bronchial infection occurred in about 25 per cent of the asthmatic patients.

* As this subject was recently published in detail in *Acta Allergologica, VIII*, 163, 1955 by SVEN BERGMAN, HELGE COLLDAHL and ERIC NILSSON, only a short summary is given here.

PORTUGUESE CRENOTHERAPY IN ASTHMA AND ALLERGIC DISEASES

by

MARIO DAMAS MORA

This address pretends only to call attention to the advantages of crenotherapeutic treatment as an adjuvant of anti-allergic therapy, and to remind you that Portugal is rich in mineral waters with properties similar to many others all over the world.

By allergy is meant—according to Messini, in the etymological sense of the word—any and every modification of the reactivity of the organism, including both the increase and the diminution of the reactive state and, therefore, anaphylaxis, atopy (Coca), idiosyncrasy, phylaxis, and even acquired immunity (Billard).

How did this conception of allergy arise?

The result of Pasteur's work, which confirmed the notion of the body accustoming itself to bacteria and their toxins, and thereby warding off the danger of a future invasion on a large scale, reminds one of the old story of King Mithridates, who, fearing to be poisoned, used to take minimum doses of poisons daily in order to become immunized against them. Hence the centuries-old term mithridatism, for the phenomenon verified by the end of last century, and later on corroborated by the utilization on a large scale of sera and vaccines as a more efficacious means of guarding against various diseases.

With the same idea in mind, Prince Albert I of Monaco, being very keen on marine biology, engaged two French biologists, Charles Richet and Paul Portier, to find out the effect of repeated doses of poison from a marine animal, *Physalia* (commonly called the 'galley' or 'marine lung') on animals in the laboratory which he had installed in his yacht Princess Alice II.

On returning to the laboratory of the Faculty of Medicine of Paris, the two investigators replaced the Physalia by *Actinea*, a sea-anemone, the poisonous extract of which, 'actinotoxin', came to be used in the immunity experiments.

A dog — called Neptune, in memory of the two scientists' sea voyages —was injected with 0.05 cc. of actinotoxin per kg. bodyweight on January 14, 1902. An hour after this injection the animal was perfectly fit. Four days later the same dose was repeated, with identical result. The animal kept perfectly bright until February 10; '... healthy, happy, active, with a glossy coat'—thus the report of the Academy of Medicine.

On the latter day—write the two scientists—at 2 o'clock in the afternoon, we injected 0 12 cc. of the toxin per kg. bodyweight. This at once produced vomiting, defective action, tremors of the front legs. The dog lay down on one side, completely lost consciousness, and died half an hour later, suffocated under the influence of this injection, which, given for the first time in this percentage to another, unsensitized dog, provoked only some sneezing and itching'.

These facts—they continue—removed all doubt we might yet have had: not only are animals, repeatedly injected with weak doses of toxins, not immunized relatively to those injected for the first time; they even appear to have been sensitized.

This newly discovered phenomenon we call *anaphylaxis*. Its revelation to a scientific world until then blindly credulous of the idea of small doses of serum or vaccines immunizing the organism, completely altered the existing axiomatic notions, and constituted, as Arnault Tzanck declared, one of the most notable milestones in modern medical science.

Richet's and Portier's communication was followed by subsequent resounding confirmation. Thus, Arthus discovered that the anaphylactic shock can be provoked by a simple, trivial injection of serum; that intradermic injection of this serum can set up a kind of phlegmon—true local anaphylaxis (phenomenon of Arthus); and Nicolle in 1906 verified that '. . . if one prepares an animal with a first injection, and injects its blood into another, non-prepared, animal, the latter in its turn becomes sensitive to a second injection'.

On the basis of these experiments, Von Pirquet explained that the human body, when in contact with any substance (dust, chemical products, foods, micro-organisms, etc.) may under certain circumstances react in a different way from the habitual one, and that this sensitivity may originate the disease. He called the sensitizing substance: Allergen, and the mutation in the organic reactions, Allergia.

Once this phenomenon was verified there occurred an entire series of surprises Sanarelli in 1924 prepared a rabbit with a non-lethal injection of some microbe. The following day he injected another microbial substance, harmless to any 'non-prepared' animal; .. and the rabbit died after a few hours, with congestion and general haemorrhage, completely unrelated to the injected products! Why? This reaction is inexplicable. Whether general or local, it will only occur with a short space of time between the two injections; i.e. not more than 72 hours, for otherwise nothing happens. It has, moreover, nothing to do with the anaphylaxis problem, for its effect is much more rapid, and it is not related to any specific substance; neither is it transmitted, as Nicolle did when inoculating the blood of a prepared animal into a 'new' animal. Neither is it an allergy, properly speaking, when we refer to the sub-

stances employed; for we can provoke a particular, different sensitiveness with each of them.

But what is beyond doubt is that this mechanism bears a resemblance to that of certain infectious diseases in man, e.g. measles, scarlet fever, smallpox, etc.

In 1928, Schwartzman reports another fact: After injection of a microbial filtered solution into a rabbit's gastric wall, followed on the next day by an intravenous injection of the same product, haemorrhage and necrosis of the local tissues set in at the point of the first puncture. And this result is constant in any organ if it is 'prepared' in the same manner!

Nevertheless, this apparent experimental simplicity is variable in accordance with heredity, climate, food, etc. of the animals, as is reported by Sulzberger at the Rockefeller Institute of New York, at the clinic of the great immunologist Karl Landsteiner. The following story is interesting in this connexion:

About the year 1927, after this reaction of sensitivity to atoxic products had been verified by Jadassohn and others, Sulzberger declares that Landsteiner was unable to obtain the same results with his guinea pigs, despite all the resources of his marvellous laboratories. The European scientists thereupon offered to teach the Americans the exact technique used in Breslau and Zürich, after making sure that the guinea pigs used were identical in size, weight and colour. Notwithstanding all their efforts, however, and great disappointment, the experiments failed, which made Landsteiner and his assistants doubtful of the truth about the experiments reported by the Europeans. For almost 4 years after this, dozens of experiments were made on guinea pigs which were sensitive in Europe, but indifferent in the United States!

At long last the conclusion was arrived at that, to produce the required sensitivity, it is necessary to include the various factors mentioned above, i.e. heredity, food, climate, products utilized, etc., in a mixture of elements lacking any defined explanation, and henceforth vaguely termed *idiosyncrasy*, or in Bard's denomination, *personal susceptibility*.

The strange sensitizing substance which we call antigen or allergen provokes the appearance of a substance contrary to the 'antibody' at the level of the live cell. The conflict antigen-antibody is frequently accompanied by a histamine discharge; a kind of organic toxin which represents what we call, in theory, the allergic reaction. Hence the application of anti-histaminic medicines which, by neutralizing the organic histamin, subdue the reaction.

In reality, however, the human diathesis goes beyond the researches of investigators and their theories, however well imagined they may be. So we sacrifice the existence of allergic individuals to these very anti-

histaminics, and other allergics to any substance on a level with any and every organ—and this justifies us in affirming that allergy is an integral part of human pathology.

New horizons are thus opened up to the physician, in the truest sense of the expression. The individual patient is an organic whole; his reactions in the face of an infirmity may sometimes assume the aspect of a local affection; but they concern the entire organism, which responds, all according to the manifestations of the disease, with especial characteristics.

It was on this basis that Selye, the wellknown endocrinologist, created his concept of *stress*: a combination of aggressivity and reactions of defense, with a corresponding state of general adaptation, with its increase or decrease of the secretions in the three phases of the morbid process: reaction of *alarm*, period of *resistance*, and state of *exhaustion*, followed by death.

Each patient is a case apart, because each one is the bearer of his own personal sensitivity; and allergy, as we have seen, is a reaction of the entire organism against anything—objects, chemicals, vapour, light, temperature, smells, dust, fabrics—in short, half of the entire milieu. This reaction of the individual is completely independent of the product that may provoke it. Its intensity and particular type are of so little consequence that my dear friend, the late specialist Arnault Tzanck, called this phenomenon *reactional pathology*.

The conception of allergy has completely modified the notion existing until recently, of a disease confined to an organ or group of organs We now consider the entire living field in which the reaction causes the whole organism, beyond the visible clinical lesion, to intervene after a period of time during which the sensitivity existed without our knowledge.

There is the case, for example, of the surgeon (referred to by Leriche), who one day, during an operation, pricked his finger through a rubber glove. Being an incident of no importance, it was forgotten, until the surgeon noticed that whenever he did any manual work, the phalanx of the pricked finger would go hot and cold for some minutes per day. Some months later he happened to hit it rather hard against some solid surface, and noticed an intense redness, followed the next day by an abscess with pus at the very point of the original puncture!

Another case is that of a woodman who, during the war, was shot in the arm The alterations of the injured nerves were conveniently treated, and the man was able to resume his normal life without any trouble whatsoever. But one day, ten years later, while sawing a tree —his usual daily job—he suddenly felt a persistent pain precisely affecting the nerves formerly hit! For ten years this man had forgotten

the accident; but his tissues, his organism, had remembered and reminded him!

There is also the very interesting story, told recently by Louis Delmas in *La médicine totale*, about the old alpinist who for seventy-one years had moved about without any painful symptom, fatigue, or limping, although he had a deformed knee that had been treated at the age of eight, and which, after all these years, without any apparent cause, has set up an enormous, extremely painful haemarthrosis, to remind him of the old alteration of the articular surfaces.

How many similar cases have we doctors not seen passing through our consulting rooms? Do alterations in the nervous circuits complex cause the organism to react at a distance under a pathological influx of the moment?

Disease—as Tzanck again affirms—is a story that cannot be told by bits, neither in space, duration, or evolution. This axiomatic notion, revolutionary in the serenity of Pasteurian medicine of the beginning of this century, confirms the essence of the theories expressed by my dear *regretted friend Auguste Lumière, theories which he expounded* so modestly in his book 'La maladie cette grande inconnue'

Having appreciated the allergic phenomena resulting from individual sensitivity, one readily understands the reason for the influence of crenotherapy in the treatment of affections of this nature. The antiallergic properties of mineral water act in a complex manner not only locally on the organ treated, but also by favouring organic disintoxication; modifying the predisposition, either hereditary or acquired, and favourable to the occurrence of allergic manifestations. Without a truly specific action, whether curative or experimental, it is unquestionable that there is an advantage in the adjuvant application of crenotherapy for the resolution of the morbid factors whether general or local.

For Doerr, Jadassohn, Diedey, Berger, Hansen and others, affections are allergic only when the existence of an antigen-antibody reaction can be proved But since this frequently eludes the best methods of investigation, we have to consider the affections, whose anamnesis and clinical observation show the characteristics of allergy and give way to the respective treatment. Let us then classify them according to the orthodoxy of the processes:

a) Purely allergic affections. They manifest themselves normally by a sericeous exanthema, or in the form of polyarthritic perturbations, myalgia, oedema, etc.; alimentary and medicinal allergies, urticaria, angioneurotic oedema, vasomotor rhinitis, hay fever, bronchial asthma, migraine, Ménière's disease, eczema, neurodermatitis, etc.,

b) Affections with an inflammatory allergic factor or an allergico-

infectious one, as glomerulonephritis, endomyocarditis, polyarthritis, tuberculosis, etc,

c) Affections in which the existence of an allergic factor can be recognized: the pregnancy toxicoses, sclerosis in plaques, gout, gastritis, gastro-enteritis, colitis, neuritis, etc.

The allergens or antigens may be classified as follows:

1) Exogenous allergens: those which penetrate the organism from outside.
2) Endogenous allergens. elaborated by the organism itself, or by bacteria existing in it (focal infections).
3) Allergens of invasion: deposited by parasites on or into the organism.
4) Physical factors: cold, heat, light, pressure, etc.

The exogenous allergens are subdivided thus:

a) Allergens by inhalation: pollen of plants, dust, various powders, etc.
b) Allergens by ingestion: foods (milk, eggs, fish, strawberries, tomatoes, artichokes, etc), and medicines (bromides, iodine, salicylates, barbiturates, sulphones, compounds of thiouracil, javel water, paraphenileudiamines, alkaloids).
c) Allergens by contact: Products of vegetable or animal origin that come into contact with the skin or the mucosa, e.g. horsehair, silks, nylons, cosmetics, rubber, etc.
d) Allergens by injection: penicillin, streptomycin, the poison from the bee's sting, of from spiders or bed bugs. This group also includes the sera and the Rhesus factor.

When prescribing a hydromineral treatment for an allergic patient it is necessary, to obtain the best results, to establish exactly the nature of the affection, the constitutional ground to be modified, and the correct application to be used. It is ignorance of these factors that is nearly always responsible for the lack of success which both disheartens the patient and discredits the waters!

Another aspect to be borne in mind is that the water cures should never be applied during an acute period of allergic crises, but only in the intervals. In the former periods, crenotherapy is usually badly tolerated, with exacerbation of the syndrome, because of the local and general reactivity normally provoked by the waters at the beginning of their being used.

Various hypotheses have been put forward for the application of mineral waters to allergic affections. Thus, Billard in 1913 tested the anti-anaphylactic effect of the bicarbonated-chlorated-carbogaseous and arsenical waters of Royat, in France, by sensitizing a laboratory animal with horse serum, and treating it daily for three weeks with subcutaneous injections of water test. After some time had passed, he verified, by a

new injection of serum, the harmlessness of this injection as compared to another, non-desensitized, test animal.

The same results were also arrived at by Flurin and Armengaud with the sulphurous waters of Cauterets; by Perrin and Abel with the bicarbonated sulpho-calcic water of Vittel, and by our countrymen Feliciano Guimaraes and Gouveia with the sulphocalcic waters of Curia. However, the latest investigations appear to confirm the hypothesis that crenotherapy effects a modification in the humoral and neuro-endocrinous system, and does not act directly on the allergic sensitizing element, which explains the identical results obtained in clinical practice, *from waters of different mineral composition* and concentration. Thus, *sulphurous waters* find a wide application in certain forms of allergic disease, particularly in bronchial asthma, in rheumatism, and in certain dermatoses, thanks to their antiphlogistic action and their trophic and protective effect on the mucous membrane, as well as being a reconstituent equilibrator of the endocrine-neuro-vegetative system, and of the metabolism of carbohydrates, in addition to the specific role which they perform in the activity of the hepatic cell, and the consequent modification of the constitutional system

Of this nature are our waters of Vizela, Taipas, Caldas da Saude, Canavezas, Molêdo do Arêgos, S. George, Entreos-Rios, S Pedro do Sul, Felgueira, Manteigas, the S Paulo baths at Lisbon, among the sulphurous sodium waters, and Caldas da Rainha among the sulphurous calcic waters. They are used by way of cutaneous immersion baths, by way of direct inhalations, and from the patients' milieu through the respiratory organs; by ingestion in the form of drinks, in genito-urinary diseases by irrigation, and by subaquatic enteroclysis.

The *chlorated sodium waters* are administered in various forms; e.g gastrically on an empty stomach, when they are indicated in allergic cases connected with gastro-entero-hepatic dysfunctions. They also act on the organic metabolism by their general disintoxicant action, by means of baths, inhalations, pulverizations, etc. This group includes the waters of Cucos, Estoril, Termas Salgades, Batalha. St. Martha, Castelo de Vide, etc.

The alkaline waters of the group called *bicarbonated alkaline-earthy, bicarbonated sulpho-alkaline, and bicarbonated earthy-sulpho-alkaline* are administered by baths, inhalations, irrigations, etc. According to several authors they 'act on allergic manifestations connected with entero-hepatic disorders, and on those of a gouty origin. In view of their calcigerous content their efficacy is notable as diuretic, antiphlogistic, remineralizing and sympaticothropic agents. Of this group, the waters of Pedras Salgadas, Vidago and Salus, Chaves, Monção and Monchique are predominantly sodium bicarbonated; those of Melgaço

and Moura are calcium bicarbonated; those of Curia and Monte Real, sulpho-calcic. The chlorated bicarbonated carbo-gaseous waters are being used with magnificent results in the treatment of bronchial asthma, in inhalations. They act on the nasal mucus and as an anti-congestive on the bronchial tubes. This group includes especially the famous French waters of Mont-Dore and Royat.

The radio-active waters have a beneficent action on allergies of a neuro-vegetative and hormonal origin, as modifiers of the organic diathesis. This group includes the waters of Abrunhosa, Alcafache, S. Gemil, Urgeiriça, Luso, and Curia, whose radioactivity generally exceeds the 2 millimicrocuries per litre, i.e. the rate demanded by Violle in his 'Actualités d'hydrologie et climatologie médicales', for a mineral water to be called radio-active.

The hydromineral waters mentioned above, which are effective in modifying the organic diathesis, are much favoured in our country; the Gerez ones are especially worth mention; being hyposaline, they contain a very high percentage of sodium fluoride, which makes them unrivalled in their kind all over Europe.

Apart from the hydromineral factor proper, one should also bear in mind the need for a satisfactory climate, and for pure air, free from allergizing factors.

Summarizing, we may affirm that:

1) Crenotherapy, by its disintoxicant action, and as a modifier of the humoral and neuro-vegetative system, is a treatment of great value, as a complement to a rational anti-allergic therapy.

2) It should never be employed during a period of acute allergic crisis.

3) To ensure its favourable result in allergic patients, there should be perfect co-operation and synchronization between the allergist and the hydrologist, so that the nature of the affection can be correctly diagnosed, the constitutional system to be modified can be determined, and the right application decided upon.

4) Portugal, by virtue of its hydro-mineral wealth, can rival any country in this respect; there only remains the necessity of creating —as I have been advocating for a long time—Centres of research and treatment of asthma and allergic diseases, where specialists may work and improve their technique of arriving at an exact diagnosis and the right application of remedies.

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LUG WORM (ARENICOLA) SENSITIVITY

by

A. W. FRANKLAND

The lug worm or lob worm (*Arenicola marina*), is a common worm found living in the sand between tide marks on the sea shore. It is often used in sea fishing as a bait The following is an account of a patient who developed a sensitivity to lug worm.

The patient was a man of 52 years, who had fished with lug worms since he was a boy. His occupation was a porter in London, but twice a week he went down to the coast to fish, on his half day holiday. In 1954 he noticed that when he went to fish at Hastings, the same evening he developed asthma. He was free at all other times. One day he decided to fish at a new place and he chose Dover. He was pleased to find that he was free of asthma after fishing there. He then remembered that he had only used mackeral fish heads at Dover as bait. He tried this bait at Hastings, but caught no fish and also for the first time after fishing there had no asthma. The next time, using lug worms at Hastings, he again developed asthma. He also found that if he went to Dover and fished with lug worms he developed asthma there too

He was sent to me as a patient who stated that lug worms caused asthma and so far as he knew nothing else. Further questioning brought to light the fact that when threading the worm on the fish hook, he had recently noticed an irritation of his fingers. An extract of lug worms was prepared. A hundred known allergic patients were tested with the extract Nine of them gave a doubtful (+) positive response. The patient gave a definite (++) positive response. All other skin tests to common allergens were negative. He has been advised to give up using lug worms as bait.

The interest in this sensitivity which has not been described previously, is more in the possible manner of absorption of the sensitizing antigen. The worms were kept in a tin The only contact with the very moist worms was when he threaded the fish hooks. Apparently it was during this time that the lug worm was in some way absorbed. This produced a local urticaria of the fingers and asthma.

STATUS ASTHMATICUS IN THE PATIENT'S HOME*

by

M. J. GUTMANN

May I ask you to depart in your minds for a while from your well equipped and smoothly functioning clinic or hospital where a mere glance at your assistant will rouse the latter to action, and where your accompanying nurse can read your wishes in your eyes and executes them implicitly. Imagine yourself in a private home of rather modest standing surrounded by the more or less excited members of the patient's family. The treating physician who had asked you to come over is absent and all you know from him is the diagnosis of 'status asthmaticus' which he mentioned on the phone.

In whatever condition the patient be, he is not capable to furnish any information and you must fall back entirely on your own faculties of perception, on your discerning eye, your keen ear, your tapping finger, sometimes even your sharp nose and eventually on your own experiences.

Remember that of all the methods appropriate in hospital, but few are applicable here. Whereas every available assistant widens the scope of your therapeutic possibilities while you are all on your own you can only do *one* thing at a time; in those serious situations that we are going to discuss the sequence of the steps you are going to undertake may prove of the greatest, sometimes even of decisive significance—therefore—first things first. You will be wise if you ask all, but one of those present to leave the room and to prepare some boiling hot water at once—for reasons which will presently become apparent. Such request will, moreover, reconcile them for having been ordered out, as they can now busy themselves with something for the patient's benefit

Situation I· Patient is unconscious

The condition is serious and seems endangering the patient's life—but there is hope—so at least you should tell the family.

The patient is reported to have been unconscious for some short time only. He is cold and clammy, in deep cyanosis, his pulse is just palpable and rapid, respiration is slowed down and failing and you think that this is the end. One glance will tell you that during the past hours the patient has received numerous adrenalin injections, perhaps he even administered them himself, judging from the syringe and the empty

* From 'Consultant in Allergy', a collection of practical experience.

ampoules that are scattered around and from the red and swollen spots on his tighs. They are the preferred place for self-administered injections, unskilfully executed, with part of the adrenalin remaining in the skin and simulating adrenalin resistance, a subject we shall return to presently. You might also find inhalation-apparatus, for adrenalin or aleudrin (isuprel) or may be one of those dangerous electric aerosol sprayers which can be operated any time without effort and without control and which are therefore frequently overapplied.

At this point you must not waste time. It is true, we know that such states of unconsciousness, of anoxemia, will sometimes pass spontaneously within a few seconds, but if they persist for more than one minute swift action is imperative. Do not let yourself be deceived into despair of futility nor should you heap indiscriminately medicines, thinking that while matters are too far gone to be upset any more you can just only win if anything.

Three things demand your immediate attention: respiration, heat and fluid supply. Remove the pillows from beneath the patient's head, until you have him flat on his back and start straight away with the 'Respiration by pressure on the diaphragma', a procedure with which you should technically be well familiarized. Clasping the patient's abdomen below the ribs between both your outstretched hands, you press the intestine upwards, thus driving air out of the rigid thorax and repeat *this movement rhythmically for some time. As soon as the first deep* breath surges up, at least, quo ad vitam, the situation has been largely brought under control.

Once respiration is established you can rub in the above mentioned 'Adrenalin-depots', as we may call them now, thus introducing appreciable dosis of adrenalin into the blood-stream. Let us remember that until now the patient could not be left alone, so we had no opportunity to prepare an injection; even before doing so, we better clean his throat with a mounted swab such as should always be ready in our emergency outfit.

Meanwhile we may have managed, with the family helping, to place hot water bottles around the patient and to feed him some hot tea with glucose (that we brought along). At this stage it depends on circumstances and subject to ones experience, whether to try injecting intravenously aminophyllin or small fractionated doses of subcutaneous adrenalin. I have repeatedly witnessed in such conditions a marked motor unrest in patients just coming round out of the unconscious state. It was then impossible to get in an intravenous injection, whereas a subcutaneous one met with no difficulty, adhering to the principle of small repeated doses of 0.1—0.2—0.3 cc. every other while, until the attack is broken (though I myself have at no time even remotely approached such doses

as E. A. Brown, (Boston) recently described a case of an asthmatic attack after aspirin where 'it took 6 hours and almost 40 cc. epinephrine to pull the patient out of this attack (each minute 0,1 cc. subcutan). It is imperative that the physician not leave the patient before he is safely out of the attack; in case the doctor is urgently bound to leave he should have a colleague take over.

What should on no account be given in situations such as these, are big single doses of epinephrine, never intravenous nor ever intracardial; no morphine or the like and no antihistamines; emetics be given no sooner that the patient has been restored to full consciousness.

Situation II: The asthmatic with orthopnoea

The patient is conscious but unable to breath except in the upright posture, deeply exhausted and gasping for air, cyanotic. The family report that until a few minutes ago he was breathing so noisy that he could be heard in all rooms, that he had quietened down now, and you can see they take this as a sign of improvement.

One glance at the patient will suffice to inform you that this is a false interpretation and a dangerous one as pointed out by Leon Unger's statement (*J.A.M.A.* 150: 562, Oct. 11, 1952) 'It is better to have a noisy patient than one who is quiet and unable to expectorate'. Here is your first task to make the patient noisy again The patient is likely to lean over a table or chair, he is bathed in sweat and highly anxious. You will hardly have a chance there to apply diaphragmatic respiration, nor will you be able to get in an i v. injection, the patient being so rigidly persistent his peculiar posture that even moving his hand for immersion into hot water will prove impracticable This latter procedure by the way, is often surprisingly successful and can be applied to the feet as well, possibly with the aid of the family

If intravenous injection is possible I prefer aminophyllin alone or composite with 1 gr sodium iodide, slowly introduced. Sometime addition of papaverin is badly tolerated, whereas morphine may even cause fatal calamity. A small dose of dolestine (pethidine) of 25–50 mgm. will relieve many patients provided tolerance for this drug has been previously asserted; we invariable give it in combination with epinephrine, even in cases which are reputably resistant to epinephrine. Similarly the antihistaminics, while aggravating bronchial asthma by just their dessicating action which we try to avoid, yet enhance the efficacy of epinephrine. This seems to be due to the antihistaminics neutralizing the histamine outpour which tends to inhibit the adrenalin, thus leaving the latter free to act.

Excellent results are often achieved by inhalating of isuprel (isodrenal) through a simple apparatus with a mask. Whereas the mask is

essential, electric operation of the apparatus is not, and the simple device can be conveniently added to the rest of the emergency equipment taken along for action against asthma. The bronchi often respond to these means when they do not longer react to adrenaline.

It is amazing to behold the relief the patient experiences after the first expectoration, as he can recline again from his standing or sitting position. In order to replace the fluids that the organism has lost and replenish liver glycogen from the liberal administration of adrenalin, warm and sweet drinks are indicated at the earliest possible time.

For the prevention of immediate relapse ACTH-gel is at present the drug of choice, and should be given whenever it is not contra-indicated for some other reason. At times, fever therapy will secure the desired end. Obviously certain circumstances must be duly considered in treating the asthmatic state such as: infancy, gravidity, hyperthyroidism, high blood pressure, etc.

In the somewhat inopportune conditions prevailing in the patients home you will do [illegible] ing to make your patient [illegible] every possible manner h[illegible] ne.

Situation III The asthmatic physician in the asthmatic state

Theoretically at least treatment of the asthmatic physician should be guided by much the same principles as that of any other patient. Actually, however, deviations occur which may easily prove detrimental to the colleague's wellfare. My own results at treating colleagues are not markedly worse then those attained with ordinary patients, for two reasons: Nowadays laymen are fairly well acquainted with the nature of their afflictions, and in a general way the means by which they can be cured; they are lacking, however, judgement as to the different possibilities presented by each particular case. Physicians usually fail similarly, when their own condition as sufferers has to be evaluated and they tend either to exaggerate or else to underestimate their case. The greatest danger is to be found in overdosage of drugs and polypragmasy, particularly in status asthmaticus.

Suppose you are called to look after an elderly colleague of, say 50–60 years of age. Be sure to find him at the electric inhalator, containing a new and even more concentrated inhalant than those in general use hitherto. Here again, empty ampoules bear witness to quantities of adrenalin having been injected already as well as intramuscular aminophyllin. Your patient gasps for air, is restless, blue-red in the face and you can see the veins on his forehead pulsating wildly. He craves for more injections or whatever remedy to grant him relief and relaxation. To watch him suffer is quite a strain on your own nerves. You remember

he had a coronary occlusion some years ago and you feel a strong urge to let him have some morphine or something of the kind. Now do not let yourself in on this. Temptation for polypragmasy is strongest on such occasions. If, on the other hand, you rapidly survey the situation critically, it will occur to you how pale he was after that last adrenalin injection, how even now he still trembles; that pressure is high in the hardened tortuous blood vessels and that every new injection can only aggrevate his condition. At this point a shot of luminal will go far way in putting your patient at ease; if you can manage to perform a venesection with some assistant's help, a blood letting of 300 cc will be most beneficial. As soon as everything is more tranquil and you have the [illegible]

features of your colleague make way to a more complacent expression. You may put up placidly with his reproaches that you should have acted more rapidly; had you given in to your first mood under the circumstances you would may have done a lot of harm.

One colleague, who was very cross with me for refusing him morphine at a critical stage, called in another colleague a few weeks later, who gave him what he demanded so emphatically. He may well have paid for this with his life, when he expired some hours afterwards No effort must be saved to impress the patient with the importance of preventing subsequent attacks. Unfortunately, your endeavours of systematic therapy are often undone by the application of all sorts of new and unwarranted means and methods.

Where their own health is concerned physicians lack discrimination, as else they should know that most of the newly recommended methods disappear from the literature within a few years and that new improved drugs are not granted permission to advertise in the medical press Each one of us knows plenty of such instances.

The proper executed therapeutic measures with colleagues should be carefully observed, since otherwise they are liable to turn harmful agents through wilful correction.

Luckily—and in order that justice be duly pronounced—there are many suffering colleagues whose co-operation greatly alleviates our work and enables us to score successes which can not be secured with the average patient.

PROBLEMS OF INVESTIGATION IN ASTHMA

A comparison between the results of experimental studies on animals and clinical studies, to gain a better insight into the pathogenesis and clinical picture of bronchial asthma

by

GOTTFRIED HOLLER

In reading this paper, I intend to briefly review what I have previously written on the subject as well as a detailed study now in the press, to be published in the Acta Neurovegetativa. This study is mainly based on the results of experimental investigations by J. Kracht and his associates as well as those of earlier studies by others on 'The control of the secretion of thyrotrophic and adrenocorticotrophic hormone', with special reference to thyrotoxicosis of emotional origin, the results having been compared with those of personal studies on cases of human bronchial asthma. The working hypothesis based on these data is chiefly intended to afford a better insight into the pathogenesis of bronchial asthma, in which the disturbed correlation between the endocrine glands probably plays the most important part.

To begin with, the fact cannot be overlooked, that allergic diseases in civilized countries all over the world are increasing to such an extent, that to-day they have frequently come to be endemic. Of these diseases, bronchial asthma, being the most distressing and troublesome of these forms of illness, which sooner or later results in incapacity for work and invalidism in the great majority of cases, deserves special attention. By my calculation, there are about 15,000 patients with asthma in Austria.

I need hardly draw attention to the fact, that an infinite number of living and inanimate substances having the character of allergens are constantly invading our organism from the outside world and that an equal number of allergens may develop endogenously from a wide variety of lesions to our own cells and tissues, which then produce auto-antibodies, giving rise to conditions of allergic and hyperergic reactivity, so that they come to be the most important factors in the pathogenesis of various forms of disease and especially in bronchial asthma.

A case in point is drug allergy, about the most common cause of which is the excessive use of penicillin and in which all kinds of conditions of allergic and hyperergic reactivity, ranging from the mildest to the most severe forms (including anaphylactic shock, periarteritis nodosa, allergic arteritis, thrombo-angiitis, dermatitis exfoliativa, bronchial asthma and other allergic diseases, classified to-day as collagen

diseases in view of their common pathogenesis), are seen to occur. My head nurse, who until that time had never shown symptoms of allergy and whose familial history was negative, was often present in rooms where penicillin was being inhaled as an aerosol Being obviously predisposed *in this regard, she was sensitized to the fungus derivative*, which I have found to be a highly effective allergenic extract, especially when used in inhalation therapy. Initially, this resulted in allergic bronchitis, which my assistant believed to be due to infection, wrongly deciding to treat this condition with inhalation of penicillin aerosols. Even the first inhalation of 100,000 U. of penicillin was followed by the appearance of typical bronchial asthma. This was subsequently associated with perioral dermatitis (involving those areas of the skin which had been covered by the breathing mask), stomatitis and glossitis. An attempt at desensitization by intradermal injection of a very small dose of penicillin (1000 U.) resulted in extremely severe anaphylactic shock. The patient's life was saved, but she continued to be highly sensitive to penicillin. In addition, the clinical picture of this patient was characterized by *the fact, that for years after the event the 24-hours' urinary* elimination of 17-ketosteroids failed to exceed the low level of approximately 6 mgm. (the physiological level in women is about 10 mgm). This was interpreted by me as evidence of hypofunction of the adrenals, *another symptom being the eosinophilia of the blood. In addition*, dysproteinaemia, an increase in the number of γ-globulins in the serum as revealed by electrophoresis and an increased erythrocyte sedimentation rate furnished evidence of hyperplasia of the reticulo-endothelial system concerned in metabolism.

The case of my head nurse has its counterpart in the guinea-pig sensitized by injections of chick albumen, which always immediately has an attack of asthma and dies from anaphylactic shock in an atmosphere charged with aerosols of chick albumen. When sufficient doses of cortisone or ACTH are injected into this animal which is susceptible to anaphylaxis, after it has been sensitized with chick albumen, it will a[illegible] aerosol. Likewise, administration of c[illegible] also that o[illegible] bronchial asthma (even the most severe type of status asthmaticus).

With my associates, I have studied the data reported in the literature and I was able to determine a diminished urinary elimination of 17-ketosteroids in the resting state in about one-third of my patients with asthma (the decrease always being most *marked following severe attacks*). The Thorn test revealed the deficiency of the pituitary-adrenocortical system (or impaired function of the adrenal cortex) in the other two-thirds. In my opinion, it is this hypofunction of the adrenal cortex

(or of the entire diencephalopituitary-adrenocortical system), which frequently is hereditary, that predisposes the patient to bronchial asthma. /One of the various functions of this general defence mechanism is to keep the production of antibodies and the attachment of antibodies to cells within suitable physiological limits by cortisone (gluco-corticoid), the hormone secreted by the normally functioning adrenal cortex, so that undesirable antigen-antibody reactions will be prevented. When this mechanism is unable to do so, as too little cortisone is available, the invasion of the body by allergens, causing excessive production of antibodies and attachment of antibodies to cells (sensitization), will inevitably result in a condition of allergic and hypergic reactivity. When the same allergen again enters the body, which chiefly occurs via the lung in bronchial asthma, this results in antigen-antibody reactions in the bronchial mucosa. An allergic inflammatory reaction, marked by tumefaction and increased secretion from the mucosa, sets in. Finally, the stricture of the bronchi is increased by a reflex spasm of the bronchial muscles (attack of asthma)

As stated previously, this condition may be controlled by treatment with cortisone (substitution therapy, bronchial asthma as a disease of adaptation in the sense of Selye), whereas it can only be controlled by ACTH, when sufficient cortisone is still available in the adrenals, its secretion being induced by this artificial stress caused by ACTH.

Even the earlier literature, published about twenty years ago, refers to the fact that a number of disturbances of endocrine correlation may be detected in bronchial asthma. Hyperthyroidism being one of the most important of these disorders, I shall briefly review this condition. The great majority of my patients with asthma showed increased basal metabolism (the increase being very marked, as much as over 80 per cent in some cases). Surprisingly, the respiratory curve showed sympathicotropic characteristics (naturally, in the intervals between attacks and when certain measures were taken to control the amount of supplemental air in the lungs). There are several facts, but particularly the increased specific dynamic action of foods (especially meat) observed in my cases, which provide evidence suggesting that the increased oxidation in this case is primarily induced by the metabolism centre in the diencephalon, which increase subsequently results in impairment of the function of certain endocrine glands Obviously, the gland most likely to be involved is the thyroid; it is the chief regulator of metabolism and impairment of its function is most likely to give rise to a marked deviation of the respiratory curve. The basal metabolic rate in acute attacks of asthma, status asthmaticus and spastic bronchitis does not afford any indication as to the intensity of the processes of oxidation. Therefore, basal metabolism was only determined when vital

capacity had attained a level of at least 2500 in women and 3000 in men.

The study of cases in human subjects has shown that exophthalmic goitre is characterized by hypofunction of the adrenal cortex to the point of atrophy, and from experimental studies on animals it is known that an increased secretion of thyrotropin and thyroxine (implying predominance of the diencephalic-pituitary-thyroid system over the diencephalic-pituitary-adrenocortical system), such as may e g be induced by emotional impulses (emotional hyperthyroidism in wild rabbits), results in more or less marked inhibition of the secretion of corticotrophin (ACTH) and cortisone as well as retrograde changes of the adrenal cortex. In my opinion, this disturbance of the synergy between the two mechanisms, the diencephalic-pituitary-thyroid system, which responds to specific stress, and the diencephalic-pituitary-adrenocortical system, which responds to a wide variety of impulses, occurs in bronchial asthma to the detriment of the latter system. The primary cause of this disturbance may be either hypofunction of the adrenal cortex or hyperfunction of the thyroid. So far, it has been impossible to sharply differentiate these two types of pathogenesis of bronchial asthma into a thyrotoxic and an asthenic form. I shall merely point out the fact that treatment in cases of bronchial asthma showing exceedingly high basal metabolic rates (over 50 per cent will only be successful when very large doses of cortisone and ACTH are administered. In addition it is of importance to know that administration of antithyroid drugs which suppress the production of thyroxine in the thyroid which results in increased secretion of thyrotropin from the anterior pituitary and in turn disturbs the balance to the detriment of the ACTH will aggravate the asthma. On the other hand, iodine, which has always been useful in the treatment of bronchial asthma, will restore the normal function of the thyroid. This inhibits the secretion of thyrotropin, some degree of synergy between the two hormones is achieved and the patient will feel relieved.

This was the only thing I wished to say regarding my studies on the role of the endocrine glands controlled by the autonomic nervous system in bronchial asthma. The nervous portion shows the known symptoms of dystonia of the autonomic nervous system (impairment of nervous control), resulting in vagotonia in the region of the bronchial tree. Nervous and humoral processes interact, the disturbed correlation between the endocrine glands causes abnormal reactivity of the autonomic nervous system, extending from the centre as far as the periphery, and this in turn further impairs the hormonal and therefore the humoral metabolic processes (the physico-chemistry of our organism). This condition may be corrected to some extent by treatment with neurotropic drugs (sympathomimetic and vagolytic agents) and also, as has

been shown by experience, by psychotherapy, so that a condition ranging from more or less transient relief to suppression of the asthma may be obtained. This is not the only result, however, for this period is also marked by a *decrease of the number of changes in intermediate metabolism*, a typical feature of severe bronchial asthma. When used correctly, neurotropic drugs and methods accordingly show favourable effects identical to those obtainable by cortisone and ACTH, as stated previously, although in this case the effects will be more persistent and more marked. There is no objection to combining the two methods with a view to obtaining the best possible results. In my experience, administration of neurotropic drugs will be even more effective in bronchial asthma, when it is combined with substitution therapy consisting in administration of cortisone.

The antigen-antibody reactions (chemical transformations) occurring *in these cases of impaired metabolism are not only dependent upon* the condition of the endocrine glands, but are also controlled by the autonomic nervous system. When the mesencephalon of an animal susceptible to anaphylaxis is blocked (e.g. by cutting the cervical spinal cord or by deep anaesthesia), the classical method of sensitization by injections of chick albumen will fail When chick albumen is injected into an animal already sensitized, this will result in fatal anaphylactic shock. To prevent this, the peripheral portion of the autonomic nervous system must be paralyzed. This experiment shows, that, once it has started, an allergic mechanism cannot be arrested by the autonomic nervous centre in the diencephalon and that antigen-antibody reactions *are, in the last resort, induced by the nerve endings of the autonomic* nervous system, its intramural syncytium.

Hibernation (anaesthesia or administration of morphine being less reliable) may be used to obtain the transient disappearance of the condition of allergic and hyperergic reactivity in cases of asthma. Apoplexy put a definite end to the respiratory disturbance of a woman, who had been affected with bronchial asthma for a period lasting several decades. On the other hand, the study of the literature shows that, as I have observed myself in some cases, head injuries (concussion of the brain) and cerebral lesions due to infection (following encephalitis) may be followed by the appearance of bronchial asthma. The subjects involved are undoubtedly predisposed individuals (deficiency of the pituitary-adrenocortical system), in whom an impulse arising from the nervous portion of the autonomic nervous system increases the hypofunction of the adrenal cortex, which has been obscured up to that point, and converts it into a clinical picture with the assistance of a temporary allergic reaction. I am bearing in mind the fact, that these cases are initially characterized by the appearance of a situational

thyrotoxicosis (Selye), corresponding with the emotional thyrotoxicosis of the wild rabbit, so that the adrenal insufficiency is primarily induced or increased by a specific stress acting on the thyroid. The above suggests that this type of disease is a thyrotoxic form of bronchial asthma. The increased basal metabolism observed in 3 personal cases provides evidence supporting the theory of a situational organic disease, predisposing the patient to an allergic reaction (bronchial asthma) by impairment of the pituitary-adrenocortical system. Hereditary factors were probably involved in only one woman, whose mother was also affected with asthma.

The clinical picture of bronchial asthma (as a collagen disease) includes symptoms of hyperplasia of the reticulo-endothelial system concerned in metabolism, such as eosinophilia of the blood (demonstrable only in the bone marrow in some cases), an increase of the number of plasma cells in the blood or bone marrow removed by sternal puncture, dysproteinaemia, an increase in the number of γ-globulins in the serum, an increased erythrocyte sedimentation rate, etc. This hyperplasia of the reticulo-endothelial tissue plays a part in the pathogenesis, for antibodies are mainly produced in the cells of the reticulo-endothelial tissue and not the circulating antibodies, but those attached to the cells are active. Therefore, the most rational method would be to reduce the fixation of antibodies to cells by saturating the reticulo-endothelial tissue with stored substances and disturbing it. This view is supported to some extent by the result obtained in treatment with nitrogen mustard, which reduced the severity of the clinical picture in some cases of bronchial asthma. Once again, the results of experimental studies on animals afford a better insight into the conditions prevailing in these cases. My associates Hammerl and Millesi injected thorotrast into guinea-pigs sensitized with chick albumen. Subsequently, re-injection or inhalation of a chick albumen aerosol failed to induce anaphylaxis in any of the animals to whom the radioactive substance had been administered The same result was obtainable with radioactive gold. It is intended to try and treat patients with asthma with a radioactive substance having a small half-life.

In cases of soil dust asthma, the form of asthma with which, in my experience, the greater part of the patients in Austria is affected, it is very useful, especially in the case of children, to transfer the patients to places situated at an altitude of over 1500 m. above sea-level, where favourable climatic and weather-conditions prevail, as soil allergens are absent in these areas. A stay at these altitudes, continued over several months or years, will result in the disappearance of the disease. In view of the large number of patients with asthma, it is a matter for the public health services to take the necessary measures and found estab-

lishments for a large number of individuals. Excellent results have been obtained in the 'Alpine Children's Sanatorium Neuegg' near Obladis (in the west of North Tyrol) in Austria. Adults, who fail to find relief in the very modern spas in Gleichenberg, Ischl and Bad-Hall, as they encounter soil allergens to which they are susceptible, I send to the places Zerfauss and Hochzerfauss (in the west of North Tyrol), to the Gorlitze (in Carinthia), St. Jakob in Deffreggental (Red Cross establishment), etc, which are free from allergens and have a favourable climate.

Literature

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TREATMENT OF BRONCHIAL ASTHMA

by

JULIO A. MORETTI

Methods of treatment may be divided into: methods used to control attacks; preventive and curative measures, used to prevent attacks in the future; the elimination of specific agents as well as predisposing or contributing causes; methods which modify allergic reactions, symptomatic medical treatment.

HOW TO CONTROL ATTACKS

Administration of small doses of a 1 per 1000 solution of adrenalin, not exceeding 0 05 ml. per injection. An effective method is to give doses of 0 02 ml. every 3–5 minutes, leaving the needle in place When it is advisable to prolong the action of the adrenalin, a deep subcutaneous injection of one-half–1 ml of an oily solution is given. One should be able to detect the first symptoms of intolerance to the drug, such as chills, tachycardia, palpitations, etc., so that it may be withdrawn and replaced by other drugs When 1 per cent adrenalin is administered by aerosol, the atomizer should be placed between the lips, with the mouth half-open, and the patient made to inhale deeply as each jet of spray is thrown. Atomization is obtained by powdered norisodrine or theophylline The secretions are fluidified by sprays of 5 per cent ammonium chloride. Sublingual administration of 10–15 drops of a 1 per 1000 solution of adrenalin is useful.

Adrenalin should never be injected too close to the surface, as its ischaemic action may give rise to scabs. Particular care should be observed in the treatment of hypertensive subjects and the blood pressure should be determined after each injection

Treatment with suppositories or injections of aminophyllin results in mental stimulation, has an action on the cardiovascular system and increases the secretion of urine. The aqueous solution used in intravenous injections varies from 20–40 per cent, no more than 0.40 g should be given per dose, twice or thrice daily. Intramuscular administration is painful. Theo [illegible] may be used alone or combined with ephedrir [illegible]

Treatment [illegible] ninistration of 0.05 g., thrice daily. In view of its congestive action, particular care should be taken in treating elderly subjects with hypertrophy of the prostate, as it may cause retention of urine. Dysmenorrhoea and nervous dusturbances may also be observed.

Magnesium sulphate has a marked bronchodilative effect. 10 ml. of a 10 per cent solution are injected intravenously. Also, 4 ml. of a 50 per cent solution may be injected intramuscularly.

Subcutaneous injections of ½—1 ml of a 1 per 1000 solution of atropine produce paralysis of the vagal nerve endings. The same can be said of belladonna

Despite their antispasmodic effects, atropine and other derivatives are characterized by the fact that they dry up the bronchial secretions, so that expectoration, already difficult, is obstructed to an even further extent.

Antihistaminics are not very effective in asthma. We believe them to be effective in cases of allergic asthma without complications. Antihistaminics are not only useful from the therapeutic, but also from the diagnostic point of view, as we can be sure that the asthma is due to allergy when they are effective.

Coramine: 5 ml , injected intravenously.

Novocaine or *Procaine:* 1 per cent solution, injected intravenously.

Ephedrin and *Phenobarbital*

50 per cent *Glucose solution, Injected intravenously.*

Bronchial aspiration, with lavage of the bronchial tree by a physiologic saline solution.

CO_2 is used to eliminate accumulated matter, in solutions of 5—10 per cent with 90—95 per cent of O_2. It should be used *with care* in cases of heart failure. It *must not* be used in pulmonary haemorrhages, severe emphysema, acute pleurisy and hypotension.

Insulin shock therapy stimulates the production of adrenaline by the adrenals.

Pneumoperitoneum elevates the diaphragm. In addition, it has a stimulating effect on the nervous system and reflexes (300—900 ml. of O_2).

Lumbar puncture a few ml. of cerebrospinal fluid are removed; the action of this procedure is obscure.

Surgical sympathetic block.

Instillations of iodine (lipiodol).

Potassium iodide increases the secretion of urine and causes elimination of sodium, retention of which aggravates the condition of patients with asthma The ingestion of chlorides is diminished. (?)

HOW TO TREAT STATUS ASTHMATICUS

When the above methods of treatment have failed, the following drugs are employed: 1 ml. of ether per kg body weight, with an equal quantity of oil, administered rectally by a thin tube. To induce sleep it should be administered within 20 minutes, and to induce semi-anaesthesia, within 1—2 hours. The dose may be repeated every 6—8 hours.

To avoid environmental factors and air-borne allergens, the patient should be hospitalized in an atmosphere free of allergens.

Oxygen alone or oxygen with helium in a proportion of 80 : 20.

It is advisable to place the patient on a water diet for some time, to eliminate food allergens. Laxatives per rectum should be given to remove food and other allergens

Intravenous injections of a 1 per 1000 physiologic saline or isotonic glucose solution of adrenalin should be given

Cases of status asthmaticus associated with hypotension, tachycardia and precordial pain should be treated with xanthine derivatives, 0.50 g. of theobromine thrice daily; aminophylline; caffeine, especially injections.

Treatment with morphine is contraindicated, as it may cause death by inhibition of the cough reflex and by reducing the excitability of the respiration centre.

Intravenous injections of 100 ml. of a 50 per cent glucose solution with 0 5 ml. of a 1 per 1000 solution of adrenaline.

One litre of an isotonic glucose or physiologic saline solution, carefully mixed with 1–2 ml. of a 1 per 1000 solution of adrenalin, the injection *should never be completed within less than one hour*

Of the 1 per 1000 solution of adrenaline, 1–2 ml., diluted 10 times, may be injected intravenously and very slowly, the injections being discontinued on the appearance of pallor, tremors, perspiration, headache or dyspnoea.

Bronchoscopic aspiration is indicated in cases in which expectoration is difficult. An average dose of 20 mg. of ACTH is injected intramuscularly every 6 hours for 48 hours; when the patient shows an improvement after this time, the doses are progressively decreased. A total dose of *400–500 mg. may be administered. Smaller doses may be injected* intravenously.

The initial dose of cortisone should be 200 mg daily, preferably administered orally, the dose being decreased subsequently, while observing the course of the disease. The patient should be placed on a suitable diet. An isotonic glucose solution should be used for dehydration, 1000–3000 ml. being administered in 24 hours.

The sodium content of the body decreases in the event of vomiting, marked sweating or profuse expectoration; treatment with physiologic saline *solution is indicated in these cases* and, when the blood volume continues to decrease, plasma should be administered to prevent hypoproteinaemia. Especial treatment is indicated when dehydration is accompanied by the excessive use of sedatives, as otherwise the patient may die.

Hypopotassaemia results from administration of excessive quantities of

glucose solution and epinephrine. The normal K content of the blood varies from 16 to 22 mgm. When the concentration is 4 mgm., respiration is weak, when it is 3 mgm. breathing is laboured and when it has diminished to 2.5 mgm. dysphagia and paralysis, associated with characteristic changes in the electrocardiogram (prolonged P—R interval, lowering of the S—T segments and faint T wave), are observed.

Treatment consists in administration of 3 g of potassium chloride or potassium citrate every 3 hours, 6 doses being given per 24 hours. The diet should contain large quantities of potassium: chicken, oats and orange juice.

Acidosis caused by vomiting or malnutrition is treated with sodium lactate, plasma or physiologic saline solutions.

Alkalosis is hardly ever observed in attacks of asthma. It is due to excessive expectoration This condition is treated with administration of 1 g. of sodium biphosphate every 3 hours or glucose given orally or intravenous injections of dextrose.

Hypoproteinaemia gives rise to the following symptoms: loss of weight, dryness of the skin and tongue, subcutaneous oedema. It is treated with plasma and injections of amino-acids combined with glucose and plasma.

Supervision of the general condition and administration of vitamins is essential

The inhalants causing the attack should be eliminated.

Abstraction of 400—500 ml. of blood is useful in some cases of asthma with cardiac complications or hypertension

PREVENTIVE TREATMENT

When one or both parents are allergic, the children should be closely observed with a view to detecting possible symptoms of allergy, such as cyclic vomiting; vomiting and diarrhoea following the ingestion of certain foods; urticaria and infantile eczema.

During pregnancy women should be warned not to eat excessive quantities of food or foods known to be highly allergenic, as sensitization of the foetus has been shown to occur via the placenta.

Marriages of allergic individuals are not advisable and if they marry, they should avoid having children, as heredity has been shown to play a decisive part in allergic conditions.

It is essential to start treatment as early as possible, as soon as the first symptoms of asthmatic crisis have been detected The patients should be shown how to give themselves injections of adrenaline, as waiting for the physician may frequently convert an ordinary asthma attack into a status asthmaticus.

Patients who have given themselves many injections of adrenalin or taken ephedrin, should be placed on a *high carbohydrate diet* or given

glucose solutions, as these drugs result in the decrease or disappearance of the hepatic glycogen. This treatment will protect the liver. To-day it is known that the serum proteins (and therefore the globulin, to which the antibodies adhere) are produced by the liver. Many authors believe that antibodies are produced only by the hepatic parenchym.

General hygiene: rest, no violent exercise or massage in severe cases. No copious meals, especially no heavy suppers.

Fried food, fats, underdone foods should be avoided No spices.

Methods of desensitization may be specific or non-specific The former is passive, when the responsible allergens are avoided or eliminated; active, when the tolerance of the patient for these allergens is increased; this may be done orally or by injections

Preparation of a trial diet should be based on (1) the omission of foods to which the patient has shown intolerance, data obtained by questioning the patient regarding his diet, (2) the elimination of foods giving positive intradermal tests, and (3) the omission of foods known to be harmful to the patient in view of his organic condition This trial diet should be accompanied by dietetic cooking, i e. the manner in which to prepare the foods, which varies from one patient to another, depending on the condition of the liver, stomach, intestine, kidneys, etc., should be accurately explained.

As this diet is to be followed for only a short time, there is no need to be concerned with balancing it.

When this basal diet results in the disappearance of the status asthmaticus, foods are added to it one by one, beginning with the least allergenic foods and continuing to omit foods causing intolerance and other reactions stated by the patient, each food being given for four days, while the patient is observed to detect the appearance of any symptoms of asthma. By this method a diet is prepared, which must be balanced from the point of view of carbohydrates, fats and proteins as well as from that of salts and vitamins, as it will have to be taken over a prolonged period. By a diet of this type the foods that actually cause the asthma may be determined.

When designing a diet and eliminating certain foods, not only should the food or foods to be omitted be accurately defined, but the way in which to avoid these foods should be carefully explained. This may be [illegible] that wheat must be omitted

biscuits, etc. Thus we will not run the risk that the patient will eat the prohibited food out of ignorance and therefore one should proceed likewise with any other food.

We believe that diets should be designed in this way. We believe standard diets to be useless.

Whenever a food is allergenic and also essential, we aim at oral desensitization by progressively increasing doses of the food, thus attempting to increase tolerance for the latter. This method frequently fails.

In addition, the patient is advised to avoid inhalants which he obviously cannot tolerate or for which he has positive tests as well as those known to be highly allergenic. Contact with animals such as dogs, cats, horses and with feathers, wool, carpets made of cowhide and lambskin, etc. should be avoided. Here, as in the trial diet, once all inhalants have been eliminated, we request the patient to get into contact with them one by one, when his position or occupation compels him to do so and the result is observed.

Methods to avoid house dust. sweeping with a moist broom or rag Careful daily cleaning of the patient's bedroom, the floor, furniture, etc. Avoid carpets, pictures, curtains, many pieces of furniture in the bedroom. The patient is requested to undress in another room. Once a week the furniture is taken out, taken apart and carefully cleaned.

Septic foci: any septic focus, whether tonsillar, dental, sinusal, appendicular, vesicular, etc. should be removed.

Non-specific desensitization: Complicated cases of asthma, with a yellowish sputum, in which a bacterial allergy is probably involved, are inoculated with stock vaccines of the Delbet broth type, the initial dose being 0.05 ml. thrice weekly, which quantity is increased with each injection up to a dose of 1 ml. Autovaccines.

Attention should be drawn to the fact that a recurrence of the attacks caused by the first injections is evidence of the effectiveness of the vaccine.

0.50 g. of Armour or Whitte's peptone are given orally one-half—one hour before meals. Daily doses of 0.1—0 3 ml. of a 50 per cent solution are administered intradermally for 15—20 days. Doses of a 5 per cent solution, increasing progressively from one-half to 5 ml., are injected intravenously at intervals of 2—3 days. Doses of a 7.5 per cent solution, increasing progressively from one-half to 10 ml., are injected intramuscularly at intervals of 2—3 days.

Autohaemotherapy consists in the injection of doses increasing progressively from 5 to 10 ml., every 48 hours. A 10 per cent solution, made up of equal parts of ordinary syrup and water, of sodium hyposulphite is administered orally in doses of 2—4 g. daily. Two g. daily or every 48 hours of a 20 per cent aqueous solution are injected intravenously.

Doses of 1 g. of magnesium hyposulphite are injected intramuscularly (10 ml. of a 10 per cent solution).

Methods acting on the product of the allergic reaction: the union of

the allergen with the reagin (antigen-antibody reaction) results in the liberation of a histamin-like substance, H substance or released substance, which is the agent ultimately responsible for the allergic reaction in the organ of shock, the bronchi in this case.

There are three methods of acting: by increasing histamin tolerance, by administering the inactivating enzyme, i.e. histaminase, or by giving synthetic antihistaminics.

Histamin: as a rule acid histamin phosphate, diluted in a physiologic saline solution until the intradermal swelling due to 0.02 ml. produces no reaction or only a minimum reaction, is used. Of this dilution, doses progressively increasing by 0.02 ml with each injection, are injected for an average period of one day until 1 ml. has been administered. When no appreciable therapeutic results have been obtained, a less strong dilution is used, the intradermal test being constantly made at the beginning of each series. To avoid possible constitutional reactions, we recommend the following method: induce an intradermal swelling prior to each dose, wait 10 minutes, and when it is equal in size or slightly larger than the previous swelling, the rest of the dose is injected subcutaneously; when it is very marked, the rest is not injected and the dose is repeated with the next injection, invariably with the same precaution.

We apply this standard to all desensitizations and thus have been able to avoid constitutional reactions, which we have never observed during the 10 years in which we have been engaged in this specialism.

We always insist that the physician should prepare the dilutions from a given histamin and that commercial 'microdose' preparations should not be used.

Histaminase is an enzyme destroying histamin, present in the organism, especially in the intestine, liver and kidneys. It may be given orally or intramuscularly for a considerable period without any, or only moderate, results being obtained

We employ a personal method, consisting in the ionization of histaminase We had our most extensive experience in lesions of the skin, in wich we obtained considerable results. Papers on this subject have been published in the April 1945—141 and November 1945—149 numbers of 'El Dia Medico Uruguayo'.

The following method was used: the positive pole, moistened with water, was placed on the posterior part of the thorax and the negative pole, with the 1 g. per 500 solution of histaminase, on the anterior part of the thorax, with a milliamperage ranging from 1 to 3, during half an hour. The usual ionization apparatus was employed.

We are collecting data for future publication, but without fear of being mistaken we can state that it is a useful and effective method. We were

able to control asthmatic attacks by ionization for half an hour in various cases.

Symptomatic medical treatment with adrenalin, ephedrin and aminophyllin has been described previously.

Benzedrine, a sympathomimetic drug stimulating the function of the brain, is administered orally after breakfast in doses of 10—20 mgm.

Calcium chloride is a substance widely used in allergic conditions, though not on a very scientific basis, as it has never been possible to obtain conclusive evidence of a decrease of the blood calcium in allergic subjects. It may be given orally, intramuscularly or intravenously and we shall not enter into a discussion of the correct dosage, as it is generally known.

Iodides increase the fluidity of the sputum. They also have an effect on fungi. The dosage of potassium iodide is 3–4 spoonfuls of a 6 per cent solution daily.

Aspirin: prior to administration, an examination should be made to determine whether the subject is not allergic to the drug; it is administered in doses of 1 g, 3 g being given daily.

Hormone preparations: thyroid and ovary. They are used in cases in which they have been found to be involved.

Vitamins: especially vitamins D and C.

Physical therapy: ultraviolet irradiation, diathermy, x-ray therapy.

IN CHILDREN

To suppress attacks on the appearance of the first symptoms:

1) Put the child to bed.

2) Administer ephedrine tablets or a preparation composed as follows:

Codeine sulphate	0.25	g.
Ephedrin sulphate	0.40	g.
Glycerin	2	drops
Syrup of cherry q.s.	120	ml.

A teaspoonful every 4 hours in children aged 3 or over; the dose is adjusted to age in younger children. 0.25 g. of syrup of ipecac may be added to the above preparation.

3) Nose-drops consisting of a slightly vasoconstrictive substance (ephedrin or neosinephrine), the child being placed in a dorsal or lateral position, with the head lowered.

4) Heated inhalations. Not to be used in summer-time or when they are unpleasant to the child.

5) Aminophyllin in the form of suppositories: 0.025–0.050 g. in 3-year-old children. If the child is sensitive to chocolate, the suppositories must not contain cocoa butter. Small quantities of barbiturates may be added to the suppositories.

6) Adrenalin by aerosol in concentrations of 1 : 1000 or 1 : 100, depending on the age of the child.

7) Injections of adrenalin if everything else fails

Attention should be drawn to two very important things: (1) the injection should not be postponed for too long a period, to prevent the crisis from being established in a permanent form, and (2) an incorrect dosage should be avoided; it is advisable to administer the smallest possible doses of adrenalin to ensure an antispasmodic effect and to prevent side-effects (nervousness, tachycardia, tremor, etc.). A 1 · 1000 aqueous solution of adrenalin is employed.

Status asthmaticus, hydration Intravenous injections of 0.0006 g. of aminophyllin per kg. body weight.

Oxygen tent; first make sure that the child does not suffer from claustrophobia.

Administration of antihistaminics is not advisable in status asthmaticus, as they 'dry up' the bronchial secretions.

The failure of treatment with adrenaline in status asthmaticus is due to the fact that it has a bronchodilative action; it does not remove the obstruction of the bronchi by secretions. These cases should be treated with syrup of ipecac, $\frac{1}{2}-1$ teaspoonful being given every hour to induce vomiting and, in addition, tepid water, which also promotes vomiting, the asthma being relieved by (1) reflex coughing; (2) ciliary action, and (3) waves of movement, a type of peristaltic. The cough acts upon the upper portion of the respiratory tract, the ciliary action at a lower level, on the finer bronchi, and the peristaltic evacuates the respiratory tract.

ACTH and cortisone.

Two teaspoonfuls of ether in 30–60 g. of oil, per rectum. Also, potassium iodide, belladonna, lobelia and stramonium

MOLD ALLERGY*

by

HOMER E. PRINCE

Airborne molds are now accepted as a common cause of respiratory allergy. The ordinary airborne mold population arises from sources in outside environments such as soil, decaying vegetation, etc. Special environments on the other hand such as damp cellars, luggage, fruits and even upholstered furniture can be definite sources of mold contact in particular instances.

Two methods are available for identification of airborne mold spores. The first or the pollen slide method is rapid and gives data comparable to pollen counts. However, molds of only a few genera including Hormodendrum, Alternaria, Fusarium, Helminthosporium and Spondylocladium, and occasionally smuts and rusts can be appreciated by the slide method. The culture plate method which employs some form of selective media for the growth of molds is more suitable for the identification of a much wider variety of molds Exposures can be made for short periods depending on anticipated incidence; I have ordinarily employed the two-minute exposure time. With the cooperation of a trained mycologist, all culturable molds can be determined even to species identification by the culture plate methods. Certain molds, particularly of the Basidiomycetes group, which group includes the smuts and rusts, cannot ordinarily be appreciated even by this method.

In general, molds are distributed throughout the entire United States. In the southern areas molds present perennial problems while in the north, counts are much lower through the winter months. In general, species of the *Dematiaceae*, particularly *Alternaria* and *Hormodendrum*, make up the greater percentage of molds found in ordinary survey studies in most areas. This is particularly true in the central and southern areas. West of the Rocky Mountains Alternaria and Hormodendrum are of somewhat less importance than in other areas. In special environments plate identification is often necessary to appreciate the true mold picture.

* The subject of mold allergy is quite broad and now embodies a sizeable number of articles in the medical literature. It is not possible for me to undertake any references to previously published articles on mold allergy in this abstract. Furthermore, it is with considerable humility that I attempt to write such a brief and incomplete article on mold allergy for a meeting in Holland where so much of the pioneer work on molds has been done by the late Dr. STORM VAN LEEUWEN and his confreres, including Dr. VAN DER WERFF and the late Dr KREMER

The following list represents the author's selection of molds for ordinary testing and treatment. This selection is based on survey findings over a period of several years:

PHYCOMYCETES
- *Rhizopus nigricans*
- *Mucor racemosus*

FUNGI IMPERFECTI
- *Dematiaceae*
  - Alternaria tenuis
  - Curvularia spicifera
  - Spondylocladium sp.
  - Helminthosporium interseminatum
  - Hormodendrum cladosporioides
  - Stemphylium botryosum
  - Nigrospora sphaerica
  - Pullularia pullulans
- *Moniliaceae*
  - Aspergillus
    - fumigatus
    - flavus
    - glaucus
    - nidulans
    - niger
    - sydowi
    - terreus
  - Botrytis cinerea
  - Gliocladium fimbriatum

FUNGI IMPERFECTI (Ctd.)
- *Moniliaceae* (Ctd.)
  - Monilia sitophila
  - Mycogone nigra
  - Paecilomyces varioti
  - Penicillium
    - atramentosum
    - biforme
    - carmino-violaceum
    - intricatum
    - luteum
    - notatum
  - Trichoderma viride
- *Sphaerioidacae*
  - Phoma herbarum
- *Tuberculariaceae*
  - Fusarium vasinfectum

ASCOMYCETES
- *Saccharomycetaceae*
  - Saccharomyces cerevisiae
- *Torulaceae*
  - Rhodotorula sp
- *Chaetomiaceae*
  - Chaetomium sp.

It is to be noted particularly that in this list molds are arranged according to their botanical classification.

Mold extracts may be prepared by the allergist for his own use if he so desires. The simplest method for practical preparation of extracts for local environments is to expose the petri dish charged with Sabouraud's medium for fifteen minutes and inoculate at room temperature. After the molds reach maturity, which frequently requires three or four weeks, the petri dish may be filled with an appropriate extraction fluid such as Hollister-Stier solution and the extraction carried out for 24 hours.

reach maturity they may be removed, dried, then extracted on a weight volume ratio in the usual manner. More recently type 33 mold extracts developed by The Association of Allergists for Mycological Investigations, Inc., have been made available commercially by the Hollister-Stier Laboratories. These extracts are very potent and possess great specificity with a minimum of nonspecific irritating qualities.

Testing with mold extracts is ordinarily carried out in much the same manner as other inhalant substances such as pollens are tested. Scratch tests with the type 33 molds are essential as a preliminary step; negative reactions may be confirmed with 1 : 1000 intradermally. Positive reactions by scratch tests should be followed with higher dilutions intradermally, often up to 1 : 100.000.

Positive mold reactions are significant if they are obtained by the scratch technique, if they are obtained in high dilution by intradermal testing, and if they are confined to botanically related molds. Systemic reactions following intradermal tests and finally beneficial results with treatment enhance the significance of mold reactions.

DISCUSSION

P. J. VAN DER WERFF

May I remind you of the fact, that Dr. Prince is one of the pioneers of fungus-allergy in America ... causes (viz. mo ...

Perhaps you ... lands.

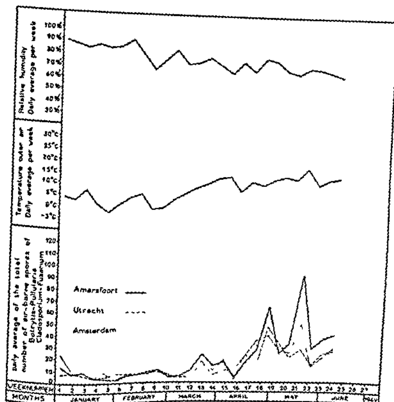


Fig 1

First I must emphasize, that each country has its own dominant mold groups ...

in Utrecht.

TABLE I

In Utrecht the counts for one year were 6345 cultivable moldspores. Duration of exposure 5 hours a month.

Bernstein & Feinberg method:

Cladosporium	31,4 %
Fusarium	7,6 %
Botrytis	3,1 %
Pullularia	2,5 %
Penicillium	30,6 %
Yeasts	21,0 %
Mucor	2,0 %
Alternaria	0,4 %
Mycelia sterilia ...	0,3 %
Trichoderma	0,27 %
Aleurisma	0,25 %

Other Fungi:
33 colonies of 13 genera

Many fungus colonies in the first stage growing as Mycelia sterilia were found to be Fusarium species when a correct cultivation technique was used: acid oatmealagar, rice, stalks of the Lupinus polyphyllus Lindl.

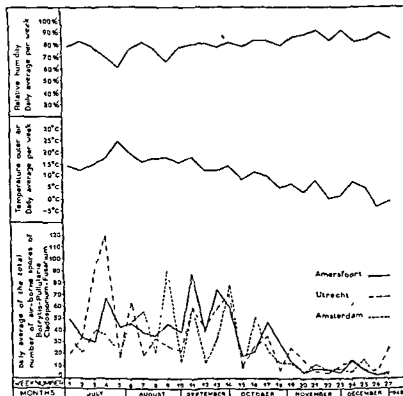


Fig. 2

No connection with weather or seasonal influences could be demonstrated regarding 2 of the dominant groups: yeasts and Penicillia

But the occurrence of the air-borne spores of a group of 4 dominant genera: viz. Cladosporium (Hormodendron), Fusarium, Botrytis and Pullularia is remarkable, showing characteristic peaks during summer and autumn (fig 1 and 2)

As can be demonstrated this fact largely depends on the temperature and relative humidity of the atmosphere outdoors

The highest peaks are mainly observed when the average daily temperature is 10° C. and over and the average humidity is 75—100 per cent.

During that period there is an increase in the frequency and intensity of acute attacks of asthma some patients being subject to attacks during that time only, others being liable to particularly severe attacks during this period, but showing minor disturbances throughout the rest of the year. These patients showed a specific mold allergy, coinciding with their seasonal periods of allergic manifestations of the respiratory tract Inclosing I wish to say to those amongst you who have a special interest in this field, that the Mold Culture Centre (Centraal Bureau voor Schimmelcultures) Head: Prof Johanna Westerdijk, & her associates a o. Dr. G. A de Vries, Javalaan, Baarn, Holland, will give any information and supply any wanted mold culture, for comparison etc.

THE RELATION OF PARTICLE SIZE TO THE ALLERGIC REACTION OF THE BRONCHI

by

K. MAUNSELL

Inhaled particles larger than 100 microns in diameter are caught by the vibrissae and expelled. Particles of a diameter of 100 to 10 microns will be deposited in the nasal fossa, pharynx and trachea. Into this category fall all pollens and larger spores and clumps of spores and medium sized dust particles to which bacteria may be attached. Particles of a diameter of 10 to 3 microns will be deposited mainly in the bronchi and bronchioles. In this range are included smaller spores, such as Penicillium and Cladosporium, and smaller dust particles. Once inhaled, these particles cannot be exhaled, because deposition takes place They are removed by ciliary action and ultimately swallowed or expelled by sneezing and coughing. Whilst they are travelling on the conveyor belt to the nasopharynx, the fully water-soluble allergens are dissolved and can react locally with the mucous membrane of the upper and lower respiratory tract. Only particles less than 3 microns in diameter, such as bacteria and fine coal dust, reach the alveoli and are exhaled in varying degrees or eliminated by phagocytosis.

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TREATMENT OF ASTHMATIC PATIENTS DURING OPERATIONS

by

W. J. QUARLES VAN UFFORD

There are various sides to the surgical treatment of patients with bronchial asthma.

I. There is a favourable side: ether is a favourite drug in the treatment of severe cases of status asthmaticus, which fail to respond to any other form of therapy; the antibacterial agents administered frequently have a favourable effect on the existing bronchitis; the operation may be regarded as a stress, which may have a favourable action.

II. There is an unfavourable side: symptoms of hypersensitiveness to procaine, etc., (treatment of headache with aspirin); administration of opiates to relieve pain; increased bronchitis due to singing; cough reflexes, especially those due to the temporary limitation of respiration; postoperative aggravation of the symptoms of asthma (attributable to a lowered general resistance, impaired ventilation of the lung (possibly associated with bronchitis), administration of drugs, change from rest to motion, change from surroundings free of dust to surroundings containing large quantities of dust after discharge from the hospital).

In view of the adverse action on the recovery from the effects of operation, *prevention* of attacks of asthma, bronchitis, etc. is indicated in these cases. This implies pre-operative treatment of possible unfavourable reactions, which may be expected to occur.

Often the two methods of treatment coincide in part:

phenergan is frequently used in premedication in modern anaesthesia; phenergan may often be used effectively to treat insomnia due to pain or even to relieve pain. One ml. is administered initially in these cases and, if need be, another ml. is given one week later.

Administration of blood and fluid by intravenous drip enables us to give aminophyllin and, if necessary, some procaine throughout the entire day.

Antibacterial treatment often is very useful, not only to prevent infections in the operative field, but also to avoid possible exacerbations of the bronchitis. Treatment is preferably started shortly prior to operation.

In addition, the patient is given pre-operative treatment in an attempt

to eliminate the symptoms of bronchitis and asthma, postoperative treatment consisting in administration of expectorants (twice a day ½ hour of treatment with steam frequently affords considerable relief) to keep the chest as 'loose' as possible, administration of anti-asthmatic drugs in the form of suppositories, if necessary, and administration of aminophyllin (combined with procaine, if need be) by intravenous drip.

Personally, I was much impressed by the treatment of surgical patients with breathing (and other) exercises in the Physiotherapeutic Department of the Brompton Hospital, as this treatment also increases ventilation. This method has not yet been generally adopted in the Netherlands This must be estimated very important.

Accordingly the following scheme of treatment is indicated:

a) avoid any unnecessary drugs (e.g. aspirin);

b) substitute phenergan for morphine, etc ;

c) to prevent possible allergic reactions to drugs, administer powerful antihistaminics when giving premedication (also administer these antihistaminics during antibacterial treatment);

d) prevent and, if necessary, rapidly treat symptoms of bronchitis.
   1) increase ventilation,
   2) antibacterial therapy,
   3) administration of expectorants, etc.

e) prevention of asthma by medical treatment often is much easier than the suppression of attacks. Therefore some aminophyllin (possibly included in the intravenous drip) should be given during the first days

f) to increase the breathing after the operation, inhalation therapy with 5 per cent carbon dioxide with oxygen, may be useful during the first 24–28 hours, several times a day.

This method of treatment was effectively used to prevent the appearance of symptoms before, during and after operation in almost all cases.

HOSPITALIZATION OF ASTHMATIC PATIENTS

by

W. J. QUARLES VAN UFFORD

Treatment of asthma has a twofold object:

I. suppression of the current attack;

II prevention of further attacks.

A patient with bronchial asthma may be hospitalized for:

a status asthmaticus.

b) a chronic bronchial asthma, in which a detailed clinical examination is advisable in view of the accessory symptoms.

c) a chronic bronchial asthma, in which the attacks of dyspnoea follow one another in rapid succession.

d) examination to determine the degree of disablement.

e) tests for certain allergic factors (district, house allergens, diet tests, psychological and social examination).

The attacks can usually be controlled by rest, the change of surroundings, administration of ACTH, euphyllin, adrenalin, etc. In that case the first object will have been attained.

The examination will also lead to conclusions regarding a possible cardiac therapy, treatment of focal infections revealed by examination, etc.

The time will come, however, when the doors of the hospital are opened wide again and the patient can return home or go to another climate or a convalescent home. This is the time when those who have only had eyes for the successful suppression of the attacks or the results of the examination meet with a great disappointment: outside the hospital, at the station, in the motor-car, during the first night at home or even later the symptoms often recur in the most severe form, if they have not been aggravated, which frequently results in another hospitalization and great disappointment to the patient.

Therefore we personally use the following method:

If necessary, the social worker employed in my practice tries to establish contact with the patient and his family during the period of hospitalization to attempt to remove possible difficulties.

Secondly, when leaving, the fact is stressed to the patient and his family that hospitalization does no[illegible] will also persist after he has left. [illegible] information regarding the natur[illegible] appointment and therefore possible reactions will be less severe.

Thirdly, the factors that will be a danger to the patient after his discharge should be determined as soon as possible after hospitalization:

a) hypersensitiveness to house dust;

b) other environmental allergens (fungi, factory dust, animals, etc.);

c) dietetic errors (particularly liable to occur when the patient is in very good health);

d) the change from more rest to more exercise.

Therefore treatment during the period of hospitalization is not only medical and generally roborant, but also consists in:

a) rapid desensitization by the house and occupational allergens, as a preliminary to the prolonged treatment at home In some cases we start with a scheme of injection, in which injections are given every 4—5 hours on the first day, every 6 hours on the second, every 8 hours on the third, every 12 hours on the fourth and then once daily, the intervals between the injections being gradually prolonged.

b) vigorous breathing exercises and kinesitherapy.

In addition, we try to accustom the patient to his own surroundings as smoothly as possible; patients never return home directly from their beds. We almost always observe a scheme of mobilization, in which the patient is allowed up in the ward for about two days, then is allowed to walk in the corridors, then allowed out of doors for a moment, then allowed to walk out of doors, then allowed longer walks out of doors and then allowed to visit his home: he has tea at home, rests at home for a moment, has a meal at home (often a more or less severe sense of constriction or dyspnoea occurs the first time and also the next evening and night), [illegible]

[illegible] quantities of dust will cause disturbances, so that during the first weeks we give the patient additional treatment at home with aminophyllin (especially suppositories) and antihistaminics In some cases the patient returns for some time to be given a gradually decreasing aerosol treatment with aleudrin and theophyllin.

We also use this scheme of adjustment after a period of elimination following high altitude and other methods of treatment.

[illegible] the mountains, followed by medical treatment during the period of transition

We believe that this scheme of treatment offered considerable advantages in our patients.

Reactions during the period of transition were highly exceptional whereas otherwise they were a common feature in these cases.

A CRITICAL VIEW OF THE TREATMENT OF BRONCHIAL ASTHMA

by

VLADIMIR SPUŽIĆ, VOJISLAV DANILOVIĆ AND SLOBODAN VUKOBRATOVIĆ

On the basis of twenty years experience of treating nearly 6000 cases of asthma, we have noticed what has already been pointed out by some others, that while in some cases we are able to interrupt the asthmatic attacks, in other instances our results are uncertain in spite of our therapeutic measures. This is in accordance with the fact that asthma is not a definite disease, but a syndrome provoked by various causes (Bezançon, [1] Pasteur-Vallery-Radot, [2] Frugoni [3] etc.), and that even the reaction, the asthmatic attack, is composed of several elements (bronchospasm, oedema, hypersecretion) combined in a very different way in each particular case. Consequently this condition is but the result of various etiologic factors.

Asthma is most frequently a disease of allergic character, the results of antigen-antibody reaction, although it can be non-allergic in character. However these two mechanisms are very often combined or substituted.

I. ALLERGIC ASTHMA

According to the majority of writers (Frugoni [4] 44.5 per cent, Castex [5] 64.9 per cent, Duchaine [6] 100 per cent) allergic asthma is of most frequent occurence. In its mechanism, which is generally very complex, one can distinguish three phases: sensitization, production of the shock tissue, and the onset of the attack. Each of these phases depends on a great number of factors. The quantity of the allergens, the contributary and localizing factors, as well as the constitution of the organism are of special importance. For the determination of the shock tissue and the declension of the attacks of already sensitive patients some other factors are also of great importance: the place and method of the penetration of the allergens into the system, the injury of the tissue, the condition of the shock tissue, and different external causes (sudden metereological changes, lesion of the mucous membrane of the bronchial tube by an infective agent or intoxication) and other factors. Because of a different pathogenesis in particular cases, it is important to determine the role of each of these factors before the necessary treatment is undertaken.

a) The quantity of allergens, i.e. constant exposure to allergens, as is well-known, is of great importance in the sensitization of the

organism and in the onset of asthma. The purpose of many methods of treating asthma is to influence this factor.

1) The elimination of harmful allergens (dust, fog, drugs).

2) The reduction of harmful allergens (improvement of housing conditions and workshops, and the sanitary improvement of the environment etc.). The isolation of the patients from a harmful environment (by change of environment, change of profession etc.). If we wish to obtain lasting results it is necessary to apply all these methods for a long time, which is not always easy. These methods usually give favourable results, but in the case of a definite predispostition the results are less favourable, since the patient is quickly sensitive to the allergens of a new environment.

b) The contributary factors, which, by injuring the mucous membranes of the bronchial tubes, facilitate the penetration of allergens, and, consequently, sensitization, are very important in the onset of an attack [illegible]

to allergy. The elimination of such factors plays an important role in the treatment of asthma. In that sense the following measures should be applied: the improvement of the sanitary conditions of workshops and houses, change of profession, appropriate climatic treatment etc.

c) The importance of localizing factors upon which depends the localization of the allergic reaction, has been pointed out in many experimental works by Vaubel, Gudzent, Halpern,[7] Spužić,[8] as well as in the clinical observations of Bezançon,[9] Frugoni,[10] Danielopolu,[11] and Jacquelin [12] The localizing factors are as follows. the way of the penetration of the allergen, and all other factors which may injure the mucous membrane of the bronchial tubes (infection, gas, etc.) and cause bronchitis. We use different methods for the relief and recovery of the shock tissue, antibiotics, autovaccines, climatic treatment, change of profession etc.

d) The immediate determining factors (presence of allergen, cold, sudden changes of temperature, various irritative gases, railway engine smoke) are of great importance in the onset of an attack. These factors which are often both contributary and localizing, are often favourably influenced by improvement of hygiene, climatic therapy, change of profession, change of locality, etc.

e) Constitution is of prime importance in asthma The factors which influence the 'terrain' are numerous and of first importance: heredity (Bray)[13] the condition of the neuro-vegetative and endocrine system (Marañon),[14] lowered inborn resistance of certain tissues (Djuričić)[15] (Parrot)[16] (Frugoni),[17] and the disturbance of the metabolism of the

histamine. It is uncertain whether the terrain is actually formed during the evolution of the disease. Coope [19] believes that the terrain undergoes changes in the course of life, and that it is strengthened or weakened. The treatment of the disturbance of the neuro-vegetative and endocrine systems, and climatic and balneologic treatment have a considerable influence on asthmatic patients. Since many factors in combination are involved in the determination of asthmatic attacks, the treatment of asthma cannot be simple or schematic.

THE VALUE OF VARIOUS METHODS OF TREATING ALLERGIC ASTHMA

In the treatment of allergic asthma the following factors are of great importance: the elimination of the harmful allergen, specific desensitization, and the elimination of contributary and localizing factors.

The elimination of harmful allergens and the isolation of the patients from a harmful environment

In some rare instances of allergic asthma, where sensitization to one allergen only is present (horses, cats, flour, ipecacuanha), after the elimination of the corresponding allergen the asthmatic attacks stop. After prolonged non-exposure to the harmful allergen, the cessation of the attacks can be permanent. Later, unfortunately, due to the individual constitution, the body may be sensitized to some other allergens, and the attacks may reappear More frequently where there is sensitization to a great number of allergens, this method is difficult to apply and the results are less satisfactory. When the patient is sensitized to a greater number of allergens and there is no possibility of the elimination of all these allergens, similar satisfactory results can often be obtained by removing the patient from a harmful environment (by change of residence, profession, region etc.).

Eliminatory diets, improvement in sanitary conditions, climatic treatment, children's homes, change of profession etc. have such an effect. In general, all these methods are satisfactory due to their lack of the corresponding allergen. The prolonged absence of an allergic reaction leads to the relief and eventually to the healing of the shock tissue. This method of treatment is the most simple, and usually gives rapid and satisfactory results, which, unfortunately, are not often lasting or permanent if the remaining harmful factors are not treated at the same time.

Specific desensitization

The specific desensitization by which one can attain the state in which the organism shows no reaction in the presence of the corresponding allergen is of great importance in the cases in which it is impossible to eliminate the harmful allergen. This is one of the most reliable methods, and actually it is the only method of treating allergic asthma.

Out of 237 cases which were under our treatment and were followed for two years or more [19, 20, 21] satisfactory results were obtained in 48 9 per cent of the cases Similar satisfactory results were obtained by some other writers. For instance Bruun [22] has also obtained satisfactory results in 59.8 per cent of the cases of asthma which he followed for a period of from 3 to 5 years. The satisfactory results which are usually obtained by means of specific desensitization are often temporary (1—3 years), and seldom of long duration or permanent. Much better results can be obtained when desensitization is prolonged or repeated According to our experience the success of specific desensitization depends on the following factors· the treatment should be begun as early as possible, in the early stages of asthma; it should be carried out without interruption for a sufficiently long period, and in respect of all the allergen to which hypersensitization exists; at the beginning of the treatment the patient should, at least for a certain time, be isolated from the harmful environment. At the same time any bronchitis which may facilitate the penetration of the allergen into the organism should be treated. Better results can be obtained from specific desensitization in cases where, there is hypersensitization to one, or to a limited number of allergens.

The mechanism of the action of specific desensitization has not yet been fully explained Most writers consider that specific desensitization increases the quantity of the antibodies, whilst Pasteur-Vallery Radot [23] believes that only a temporary accomodation to the harmful allergen can be obtained by this method.

The rush desensitization is more quickly effective, but is frequently followed by untoward reactions.

The elimination of contributary factors

The elimination or reduction of contributary factors (humidity, dust, smoke, factory gases etc.) generally has a favourable effect on the bronchial mucous membrane, and thus diminishes the possibility of the penetration of allergens to the sensitized tissues

The contributary factors can be modified by a number of methods: improvement of hygienic conditions in workshops, houses and locations change of profession, climatic treatment, residence in institutions for asthmatic people etc as well as by the application of antibiotics.

The favourable influence of an improvement in hygienic condit

antibiotics. Their significance has been more strongly emphasized in recent times

The mode of action of antibiotics is a scomplex, as is that of the bacteria on which the antibiotics act. The antibiotics (penicillin, terramycin,

aureomycine) through their effect on bacteria, reduce or eliminate the harmful antigen in cases where sensitization to bacteria exists, while in other cases they act on bacteria which are contributary or localizing factors. In 550 cases of asthma which were treated with antibiotics, favourable results were obtained in the majority of cases. Especially good results were obtained in asthmatic children (79 per cent),[24] while the results obtained in adults where chronic changes of the bronchial tubes still existed were found to be less satisfactory (65 per cent).[25] In accordance with the results of Findensein[26] we have obtained better results in cases in which aerosol treatment was applied. According to our experience, as has been stated by Pasteur Vallery-Radot,[27] the best effect of antibiotics was noticed when they were administered during Spring or Autumn, when bronchitis occurs most frequently. Unfortunately the favourable effect of antibiotics is usually of short duration, and lasts only while they are administered, or for some months after the discontinuance of the treatment. As the favourable effect of antibiotics is of short duration they should be used at the first onset of the infection of the respiratory organs, and in all early cases of asthma. The treatment with antibiotics should be repeated, and, if necessary, combined with other methods of treatment e.g. autovaccin. Thus we succeeded in preventing the onset of asthma for many years in some cases. However this means that they usually constitute only a supplementary treatment.

The elimination of localizing factors

The elimination or reduction of localizing factors which are often the same as contributary factors, but of much greater intensity, can reduce the sensitivity and can sometimes lead to the recovery of the shock tissue. Many of the above-mentioned methods of treatment may lead to these results: sanitation, climatic treatment, vaccines, antibiotics, etc.

a) Sanitation is of great importance in solving this problem. The experience accumulated during our studies of allergic patients who were working in various factories (silk,[28] stuff,[29] asbestos,[30] glass,[31] tobacco, rubber and leather[32] etc.) shows that humidity and sudden changes of temperature have a decided effect on the onset of asthma, and that the elimination of these factors contributes to the disappearance of asthma. This is best illustrated by the fact that all the women workers in one spinning mill, who often fell ill with bronchitis and asthma while working in premises with a high temperature and a high humidity, had no more attacks as soon as they left these premises, although the causal silk allergen was present in abundance. We have also established that sanitation (canalization,[32] and the construction of dams against floods)[33] have a very favourable effect on the reduction of asthmatic cases in these regions.

b) Climatic treatment (sea and altitude) have also a good effect on the elimination of harmful allergens, and on environmental factors, such as fog, dust, humidity, winds etc. With the disappearance of allergic reactions the shock tissue recovers, sometimes so well that later it does not react by asthmatic attacks to the presence of the causal allergen. Blaumoutier, [34] Pasteur Vallery-Radot, [35] and Turban, [36] Spengler and others have established the favourable effects of a high-altitude climate, which is confirmed by our experience. The high-altitude climate has an especially good effect if certain conditions are fulfilled: the localities must be protected from winds, fog, etc. The climate of the Dalmatian coast has a similar favourable effect. In 653 cases of asthma in children [37] and in adults [38] we obtained especially satisfactory results in 75 per cent of the cases treated on the Dalmatian coast. Unfortunately in most cases this favourable result was not of long duration. The effect of the sea and a high altitude climate is much more effective in early cases of asthma, and when the climatic treatment has lasted for a longer time, at least for some months.

c) Balneologic treatment, in addition to the fact that it acts in the same way as climatic treatment, by removing the allergen and relieving the shock tissue, has a favourable and direct effect on the effected tissue of the bronchial tubes, as has been established by Villaret, Bezançon, [39] Santenoise, [40] etc.

d) The effect of vaccines and autovaccines and many other treatments of asthma, climotherapy, antibiotics etc. is complex In some cases the autovaccine causes specific or non-specific desensitization. Further, by its action on chronic changes of the bronchial tubes, as a stimulating treatment, it decreases the effect of contributary and localizing factors.

The satisfactory effect of vaccines and autovaccines has been stressed by many writers (Haibe, [41] Harley, [42] Božović. [43] while Diaz [44] obtained a favourable effect in 63 per cent cases, we had only 48 per cent satisfactory results in 380 cases of bronchial asthma which were treated with autovaccines. But in most of these cases these favourable effects were of short duration, a few weeks or months, and rarely for a longer period—two years or more—and total recovery was obtained only in a limited number of cases. Since this favourable reaction is often only temporary, the autovaccine should be repeated, especially in the autumn, as has been already suggested by Pasteur Vallery-Radot and Blaumoutier. As exclusive treatment with autovaccine is usually insufficient, it is necessary to combine it with other methods of treatment (antibiotics etc.).

As one can see, all the above-mentioned methods of treating asthma do not have a favourable effect in all cases. However, the favourable effect is in most of these methods only temporary. Since these methods

give satisfactory results in early cases, it is necessary to start the treatment as soon as possible, and to apply it systematically by combining the above-mentioned methods of treatment.

II. NON-ALLERGIC ASTHMA

This group includes all cases of asthma which are not proved to be of allergic nature. It is uncertain whether all cases of asthma belonging to this group are caused by the same mechanism, Dowall [45] has shown that bronchospasm can be caused by various stimuli: irritation by gases (CO_2, SO_2 etc.), changes in potassium, calcium, and the other blood electrolytes, direct irritation by histamine or peptones, as well as by reflectory or psychical stimuli Nevertheless the mechanism of an asthmatic attack has not yet been precisely established. In non-allergic asthma the important factors are: bronchospasm, oedema and hypersecretion of the mucous membrane of the bronchial tubes. In allergic asthma, as we have seen, these changes are determined by an antigen-antibody reaction, i.e. H-substances which result from this reaction. According to Rackemann [46] H-substances have an effect in non-allergic asthma also. Actually the action of H-substances is very complex and insufficiently studied Some writers consider that H-substances have an effect on the capillary permeability, smooth muscles, and bronchial secretions in non-allergic asthma also. Dowall [47] has shown that with the reduction of sodium in the cells, as occurs when there is insufficient adrenal cortex, the smooth muscles become sensitive to histamin. According to Stern [48] histamin has an action mainly on the cells which contain much diaminooxidae, which is later the recipient for histamin. Parrot [49] found that the serum of an asthmatic patient has a lowered histaminopexic power, i e. it does not absorb the histamin which reaches the blood. On the basis of the above-mentioned facts one could suppose that the increase of histamin in the blood has a stimulating action on the cells of the tissues which contain more diamonoxidae. However, although all this points to the importance of H-substances, the mode of their formation and action has not yet been definitely settled. Besides, it is uncertain whether H-substances play a role in all cases of non-allergic asthma, perhaps this kind of asthma is caused by some other mechanism According to many writers (Danielopolu, [50] Santenoise [51]), in non-allergic as well as in allergic asthma the local distonies of the neuro-vegetative system play an important part, while some writers (Dowall, [52] Serafini [53]) consider that changes in the electrolytes of the plasma play an important part by their direct action on the neuro-vegetative system and the smooth bronchial muscles. However, the possibility cannot be excluded that even in these cases the changes

are caused by H-substances Accordingly it appears that there ought to be no difference between allergic and non-allergic asthma.

In non-allergic asthma the factors which have been mentioned in our

endrocrine systems and the resistance of the connective tissue are of great importance. The contributary factors in non-allergic asthma in general are the same as in allergic asthma, but here they play a different role: instead of facilitating the penetration of allergens they allow the harmful factors to act on the reacting shock tissues. The localizing factors, with the resulting tissular lesions, will determine the tissue which will react in the case of non-allergic asthma also.

In spite of the fact that the causes and mechanisms which lead to an attack of non-allergic asthma are different, and in view of the fact that the reaction—an asthmatic attack—is usually more or less the same in all cases, it is possible to apply some common methods of treating non-allergic asthma.

Methods of treating the symptoms of an asthmatic attack

In the cases where we are not able to explain the causes of an asthmatic attack, both in allergic and non-allergic asthma, we must use methods which have an effect on the changes themselves which determine the attack, i.e bronchospasm, oedema and hypersecretion. Since the causes which lead to an asthmatic attack are the expression of a local distonism, the sympaticomimetic or parasympaticolytic substances may be used with success: adrenalin, aleudrin, ephedrin, atropine etc. It is known that these drugs are of great value, but only in interrupting an asthmatic attack, and that their immoderate use can cause an aggravation of the condition.

Theophyllin and its derivates have a very favourable effect on asthmatic attacks, especially when used with aerosole (Pasteur Vallery-Radot). [54]

In 42 per cent cases we have obtained satisfactory results with anti-*histamine substances,* [55] *which prevent untoward manifestations caused* by histamin, however Frugoni [56] and Serafini have obtained 40–50 per cent good results, and Pasteur Vallery-Radot [57] and his co-workers in 66 per cent of their cases.

In severe asthmatic attacks, satisfactory results can be obtained by using hormones, ACTH and cortisone In accordance with the results of Pasteur Vallery-Radot and his co-workers, the result we have obtained have proved to be satisfactory. In 55 cases of severe asthmatic attacks treated with these hormones, in accordance with some other writers, we obtained favourable, but temporary, results in 83 per cent of the cases [58]

The method of action of ACTH and cortisone has not yet been established. Quarles van Ufford considers that adrenalin cortex does not play an important role in allergy, and that it acts only on one of the many disturbances of the endocrine glands which exist in allergic conditions.

Non-specific desensitization
Experience has shown that some substances, such as pepton, serum, milk, tuberculin, calcium and magnesium sulphate, can have a favourable attack on asthma. The mode of their action in asthma is explained by coloidoclassical shock, and by a following refractory period. However, these substances are unreliable and not much used.

Pyrotherapy
A temperature artificially provoked by preparations of sulphur, vaccines etc. can, in some cases, stop severe asthmatic attacks (Storm van Leeuwen,[60] Vuletić).[61]

Physical treatment
Physical treatment (X-rays, ultrasone, ultraviolet rays, diathermy) which most frequently acts like non-specific desensitization, does not give definite results. X-ray treatment, from which Pasteur Vallery-Radot and Blaumoutier[62] have obtained excellent results in 23 per cent of their cases, and improvement in 41 per cent has been shown to be of less value in our cases (36 per cent).[63]

Psychotherapy
Although the psychic condition is of great importance in the constitution of asthmatic patients, as was stated by Hansen,[64] there is actually no asthma of psychic origin. According to our experience,[65] the asthmatic condition has an influence on the psychic condition of the patient, it is obvious that later it can cause an asthmatic attack in the event of an emotional disturbance. According to Diaz,[66] emotional disturbances, as well as sudden metereologic changes, can cause an asthmatic attack. The results which have been obtained so far with psychotherapy show that this is only a supplementary factor.

Surgical treatment
Leriche,[67] Goebell, Jakovljecić,[68] Putnik, and some other writers have obtained encouraging results in the improvement of 25–50 per cent of their cases when they used the method of the infiltration of ganglium stellatum, [illegible]
[illegible]
[illegible]
often unpleasant are the main reasons why the surgical treatment of

asthma is not frequently applied, as has been stressed by Leriche in the Second International Congress on Asthma at Mont-Dore.

The surgical treatment of focal infections (inflamed tonsils, sinuses etc) actually belongs to the treatment of asthma based on the elimination of the causal allergen.

In non-allergic asthma, the elimination or reduction of contributary factors—dust, humidity, fog, sudden barometric changes—also plays an important role in the treatment of asthma. This can be obtained by climatic and balneologic treatment, sanitation, housing conditions, workshops, localities, change of residence and profession etc.

Conclusion

As has been seen, many of the above-mentioned methods of treating asthma have a favourable effect in the majority of cases (30 – 60 per cent). In some cases the favourable results can be obtained easily, simply by the elimination of harmful objects, or the removal of the patient from an unwholesome environment, in other cases, however, they are not easily obtained. This favourable effect is in the majority of cases only temporary, so that cases of complete recovery are very rare, even when the results are entirely satisfactory. Therefore even in early and relatively mild cases of asthma, and still more in long-standing cases, it is difficult to see the success of the treatment. In this respect it is very difficult to find any other disease which can be compared with asthma. This is the explanation of the prevailing opinion that asthma is an 'incurable' disease. The uncertain results of the treatment of asthma are mainly due to the great complexity of the mechanisms of this disease, and the large number of extrinsic and intrinsic factors which determine the manifestation of early and late asthmatic attacks. It has been mentioned already that besides an asthma of allergic nature, the mechanism of which is already very complex, especially if one takes into consideration the treatment by antihistamines, there is also an asthma of non-allergic character with different mechanisms, where at least in some instances histamin plays an important role. The constitution (terrain) which plays a significant role in all these mechanisms, has not yet been sufficiently studied. The role of many extrinsic factors which play an important part in sensitization, formation of shock tissue, and the determination of asthmatic attacks is by no means less clear.

For these reasons, in order to make the treatment of every case of asthma rational and successful, it is necessary not only to establish the diagnosis of asthma, but also to appreciate the mechanism of an attack, and all other factors which co-operate in the determination of an asthmatic attack. However this is not possible in all cases, even in specialized institutions The complexity of the etio-pathogenesis of

asthma and the uncertainty of its treatment are the main reasons, among others, for the scientific discussion of the treatment of asthma, and the organisation of associations of specialists in asthma.

On the basis of our experience and results, which are confirmed by other writers on the treatment of asthma, the following general principles are suggested:

1) The success of the treatment of asthma, as well of other diseases, depends in the first place on an early diagnosis and treatment in due time. Many latent forms of asthma frequently remain unknown for a long time, or they are not at first thought to be serious, accordingly, a correct and vigorous treatment, which, if applied at the proper time would lead to more satisfactory results, is not applied. If systematic treatment is not applied at the beginning, mild and reversible changes of the mucous membrane of the bronchial tubes, and the local distony of the neurovegetative system, which are followed later by psychical changes in the patient, and, finally, by permanent changes such as chronic bronchitis, emphysema, and cor pulmonale may occur. Frequently the spontaneous cure of infantile asthma, and the favourable results when treatment is applied early justify the fact that the greatest care should be given to the treatment of asthma in children, young persons, and in general in all early cases of asthma

2) In view of the fact that asthma is but an expression of a large number of different factors, the principle of the treatment of asthma must be such as to influence all factors at the same time. In this sense, for instance, we combine the specific desensitization with the temporary removal of the patient from an unwholesome environment; and if necessary we treat contributary factors, such as bronchitis, with antibiotics, autovaccines etc. These methods are used successively or contemporaneously according to the severity of the asthmatic case.

3) Due to the fact that we are never certain of permanent and total cure, the treatment should not be discontinued immediately after the first satisfactory results, which are only temporary. Many of our cases show that the disappearance of asthmatic attacks does not mean that the sensitization has disappeared, nor that shock tissue has been cured. Under new, favourable conditions further asthmatic attacks may supervene after a longer time. For this reason, even the successful cases should be kept under constant observation and closely controlled; and should the slightest signs of aggravation appear, vigorous intervention should be undertaken. Due to such procedure, many cases of severe asthma have been practically permanently cured.

Although these three principles in the treatment of asthma are of importance in all cases, there are, nevertheless, some methods of treat-

ment which correspond to various ages are of particular importance. For instance, while climatic treatment relieves all cases, in infantile asthma antibiotics are of great value. In adults, and in occupational asthma, besides specific desensitization, sanitation is very important. In old persons with complicated asthma symptomatic treatment has a special value.

From all the above-mentioned facts, one can conclude that an early treatment of asthma should be continued in which various methods are combined. This, however, is rather expensive. Hence an appropriate treatment is in many cases impossible, and, unfortunately, it is usually palliative, so that the disease is more and more neglected and difficult to cure.

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PULMONARY MYCOSIS WITH AND WITHOUT ASTHMA

by

P. J. VAN DER WERFF

A short survey will be given of 8 patients with mold growth in the respiratory tract and one case report is presented more in detail They illustrate certain aspects of occurrence and significance of bronchomycosis in relation to bronchial asthma and in connection with the therapy, especially in this respect the antibiotics.

It is conceivable that a.o. the allergic skinreaction, immediate type, may prove to be of value to the diagnostician in distinguishing between genuine bronchial asthma secondary to bronchomycosis and: the non-allergic asthmalike wheezing symptoms, such as in cases of tuberculosis, pseudotuberculosis by chronic pneumonomycosis, malignant tumors, etc.

1) As some of you, who were present at the Round Table Meeting two years ago here in Utrecht perhaps will remember, I told you the story of a patient, who in his youth worked on a cucumberfarm.

He had a bronchomycosis, infiltrative and fibrotic changes and [illegible]

[illegible] to be of no avail

The treatment with intravenous Neosalvarsan had yielded excellent result in clearing the mycotic infection; his chronic asthmatic and bronchitic complaints discontinued.

2) The second case was a farmer, no known allergies in family, whose first attack of asthma and bronchitis symptoms simultaneously occurred while harvesting rye. [1]

Together with a pulmonary infection with Staphylococcus aureus, he had a mycotic pneumonitis giving rise to asthmatic attacks as secondary manifestation, caused by an allergy to a yeast—classified as a new species of the genus Trichosporon, now called Tr. Behrendii Lodder et van Rij (fig 1).

The administration of Penicillin as an antibiotic against the bacteria made the patient worse, as it was accompanied by an aggravation of symptoms.

Rapidly his condition showed definite improvement on potassium iodide, creosote and intravenous Neosalvarsan.

[1] These two patients were discussed in *Ann Allergy, 11*, 567, 1953.

In the University Clinic for Internal Medicine, Leyden (Head: Prof. Dr. J. Mulder) we saw during the last 4 years still more patients with mycotic infections involving the bronchi or areas of lung parenchyma, but these 4 cases did not show an allergic sensitization to the fungi chronically present in the respiratory tract.

3) A farmer with chronic pneumonitis especially in the right lung. The sputum culture gave many colonies of Aspergillus fumigatus

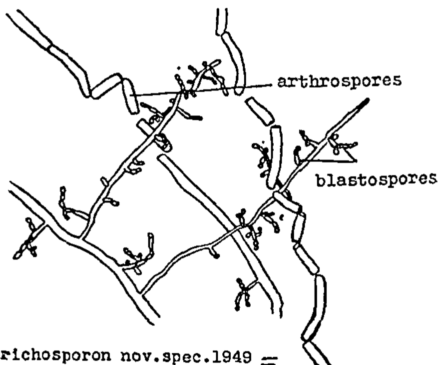


Fig 1

Fresenius. Bacteriological findings were inadequate to the clinical manifestations. He improved with intravenous Neosalvarsan.

4) An agriculturist's wife with a large cavity in left upper lung with growth of an abnormal variety of the species Aspergillus fumigatus. In the first stage this was a silent case, but later on recurrent hemoptesis established itself. Operation was indicated at that time.

5) A housewife being in poor general condition got a tonsillar fungus infection, followed by miliary dissemination with Candida albicans (Robin) Berkhout, after a high dosage cure with Chloromycetin. She died.

5a) An administrator got a tonsillar fungus infection, too, in the same way. He improved with local application of Neosalvarsan-glycerin.

6) A gardener with indurative pneumonia. His sputum contained large amounts of Aspergillus fumigatus and of the new spec. Trichosporon Behrendii. With intravenous administration of Neosalvarsan, beneficial results were gained quickly.

Later on in my Amsterdam clinic we had two clear examples of secondary thrush of the bronchi, causing characteristic allergic symptoms in one of them. These two patients were sent to Prof. Mulder, Leyden, for further analysis:

7) A farmer with chronic *asthmatoid*-bronchitic manifestations, hemoptesis, gradual aggravation of his complaints of coughing, dyspnoea, tightness in his chest and loss of weight. He had a carcinoma solidum of the right main bronchus, with an enormous thrush due to Candida albicans. His allergic skintests and provocative-inhalation tests were all negative.

8) A stock farmer with positive allergic family history, who since 2 years had a chronic cough, since about 1 year rhinitis vasomotoria and asthma bronchiale, was hospitalized in very poor general condition. He had carcinoma cardiae ventriculi with metastases in both lungs, the latter secondary infected by Trichosporon cutaneum (de Beurmann, Gougerot et Vaucher) Ota and Aspergillus nidulans (Eidam) Winter; and moreover T.B. Mycobacteria, bovine variety, were found in pleural exudation at both sides. After allergic investigations and treatment with potassium iodide and creosote the allergic manifestations discontinued together with a nearly complete disappearance of the fungi. So we felt justified in concluding that the chronic presence of the fungi started the allergic symptoms of the whole respiratory tract

9) Only one patient I would like to present to you today more in detail, because this case illustrates certain aspects of the clinical findings, diagnosis and treatment. He is a baker's son, with positive allergy in family history, who had recurrent and increasing asthmatic bronchitis since his childhood When he was first seen by us, he was 12 years old. He had allergic skinreactions, markedly strong positive for eggs, chocolate, milk, fish, wheat- and rye-flour, several yeasts and quite a lot of molds, among others those, which are characteristic as defilements for flour, (Rhizopus arrhizus Fischer, Rhizopus nigricans Ehrenberg, Mucor racemosus Fresenius, Mucor spinosus v. Tieghem, Thamnidium elegans Link). Treatment with anti-allergic diet and desensitization against the inhalants gave a rapid improvement. After 3 months he had no complaints any more. After reaching a rather high dosage, the desensibilization injection-cure was gradually discontinued 6 months afterwards.

The patient showed a perfect health during nearly 3 years, also while working in the bakeryshop of his father. He came back with complaints of very heavy tickle-coughing spells, now and then expectoration of abundant amounts of milky-whitish sputum, lancinating pains in his chest, especially at the right side, no genuine asthmatic attacks, no fever at all; these complaints were lasting about 4 months. As was told to us, all troubles had failed to respond to any treatment during that time. When staying out of the bakery, he could not find any improvement of his complaints. His recent history revealed that these troubles started, when during two weeks in summertime he helped his uncle, a farmer, in harvesting hay. Intracutaneous and inhalation-provocative allergen tests were negative. Antireagins to yeasts and molds could be demonstrated. The corrected sedimentation rate was 36 mm. one hour, 80 mm. two hours, other bloodfindings disclosed no pathologic changes; sputum contained moderate amounts of eosinophiles, and Haemophili influenzae, a few pneumococci of high type and a considerable amount of mycelium threads, falling to pieces namely in arthrospores, and with blastospores; mycological examination disclosed for the third time in a few years the new spec. Trichosporon Behrendii. The chest x-rays November 9th, 1953 (fig. 2 and 3) gave especially in the right lower chest a paracardial, intensively marked picture, with an increased density lying in a lung-segment at the front side. After treatment with potassium iodide and creosote, his condition improved quickly together with the findings in his sputum. After 4 weeks, the check-up of the sputum revealed no yeast substances any more, still a few pneumococci, but more haemophili than before.

The chest x-rays made at about the same time December 8th, 1953, (fig. 4), showed significant decreasing of the pneumonic infiltration. The chest x-rays of March 17th, 1954, gave only slight fibrotic changes in the right lower lung lobe.

Referring to the bacterial infection, learned by similar observation (case no. 2) and by the 2 cases of Leyden, I did not give any 'antibiotics' during the first time of the antimycotic cure for fear of the possibility to activate indirectly the fungal infection. Afterwards antibacterial therapy appeared to be unnecessary, since he had no symptoms and no sputum any more.

Comment

Apparently being not as rare as mostly hitherto considered, this paper was presented first in order to demonstrate *the possibility of active cases of bronchomycosis* as one of the many causal factors of asthmatic or asthmatoid symptoms and in cases of subacute or chronic bronchitis, bronchopneumonia, indurative pneumonia or chronic pneumonitis,



Fig 2
X-ray 9 XI 1953



Fig 3
X-ray 9 XI 1953

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ADDITIONAL LECTURES

ALLERGOLOGY AS A BASAL SCIENCE AND AS AN INDEPENDENT SPECIALISM *

by

H. A. E. VAN DISHOECK

In modern medicine, the doctrine and study of allergy has won for itself a recognized position; as a basal science in many different specialisms; as an auxiliary science in the performance of special techniques, and also as an independent specialism with respect to a certain group of affections. This result has been obtained thanks to a small group of enthusiastic experimenters and clinicists, who, however, had to overcome an unusually strong resistance.

The first observations concerning allergic diseases date back to remote antiquity. But it was not until 1873 that Blackley discovered the cutaneous reaction to pollen in hay fever patients. With this, the connection was demonstrated ad oculos, for the first time, between a seemingly innocuous substance and human allergy. Blackley thereby became the first clinical allergist.

His contemporaries failed to realize the fundamental importance of this discovery. On the contrary; under the influence of Pasteur's and Koch's discoveries, it was thought that hay fever, too, was probably a bacterial affection. Here, an analogy with our own times at once suggests itself: under the influence of psychosomatic medicine, many physicians tend to regard asthma, and even hay fever, as psychogenic in origin. Such one-sided exaggerations are understandible, because both infection and mental factors play a considerable part in allergic affections.

Not until the development of the immunity theory by E. von Behring and, more particularly, the discovery of anaphylaxia by Richet—now fifty years ago—did the doctrine of specific hypersensitiveness penetrate to the clinic. Richet had demonstrated that an animal can be sensitized by injection of a relatively harmless substance, and that re-injection of a small quantity of the same substance may be followed by severe phenomena such as asthma. This soon caused the medical profession —encouraged, moreover, by Dunbar's writings—to set aside any linger- [illegible]

Specialization, also in the case of allergy, is the unavoidable result of the ever progressing widening and deepening of our knowledge. That

* Lecture held at the Opening Ceremony. Prof. VAN DISHOECK, president of the Dutch Society of Allergy, was president of the Executive Committee.

which, fifty years ago, was an isolated observation, and a group of diseases against which physicians were powerless, has become a science and technique which can hardly be mastered any longer by a single individual The narrowing-down of one's interests that may be the consequence of unduly far-reaching specialization is often—and quite rightly—railed at; but we are equally justified in pointing with gratitude to scientific discoveries which humanity owes to this same specialization. The true specialist is he, who concentrates on some part of medical science, but who—just as consciously—keeps an open mind and a broad vision for those facets in other specialisms which are necessary for the understanding and the growth of his own subject. This entails the need for contact with other specialists, and team-work.

The modern hospital, with its many departments and laboratories, is the realization of this growth of specialization and integration. Here, organologists have their own, rounded-off field of activity. Characteristic of these specialists is their engrossment in the basal sciences, and their great need of assistance from other specialisms. Especially the rhinologist, the lung-specialist, and the dermatologist have been led to study allergy. Some have acquired the necessary knowledge by themselves; others had recourse to the assistance of a professional allergist. In this way, allergology has gone through a development similar to that of haematology, endocrinology, and bacteriology.

In most cases these specialisms, although not bound to one particular organ, nevertheless have some separate disease on which they focus their attention One might even say that a specialism may owe its existence to some particular disease which is both frequent and difficult to cure. Such, for instance, is the cas [illegible] allergology. If asthma [illegible] no demand for an independent allergist. In that case, allergology would have remained, like bacteriology, a basal science in each specialism. Asthma, therefore, caused allergology to grow into an independent specialism.

In common with bacteriology, allergology largely owes its scientific development to the laboratory. In the beginning, both served in the clinic as basal sciences and as auxiliary sciences. Bacteriology, however, is the clinicist's basal science to such a degree that the bacteriological specialist has his place exclusively in the laboratory, whereas the allergic specialist has found his place at the sickbed, and even, here and there, already in a department of his own. The time when this was otherwise is still fairly recent; and even now, allergology's struggle for its rightful place has not been brought to a succesful issue everywhere. It is doubtful whether any other specialism has encountered greater difficulty in the fight for its independence

This resistance against allergology is not merely the usual reaction against everything that is new and stems from the laboratory. Quite rightly, novel theories of this kind must first prove their practical value, before they can expect to find general acceptance. Thus, allergology had to prove that specific sensitization plays an important part in a disease like asthma, that the causative allergen can be traced, and that elimination of this allergen, or desensitization, can cure the patient. This assignment amounts to the demonstration that the anaphylactic experiment is applicable to the allergic attacks. The question now is, whether allergology has been found wanting in the performance of this task.

There is one disease in which this connection is as plain as a pikestaff, and which, in fact, may serve as an example of a purely allergic affection. This is hay fever. For, both the nasal symptoms and the asthmatic trouble which constitute the hay fever syndrome, are known to be caused by a well-known allergen, grass-pollen. In the absence of this allergen—as in wintertime—the morbid symptoms disappear, and the patient is a normal person again. Exposure to the allergen—also in wintertime—will at once cause the recurrence of the symptoms. No wonder, therefore, that the doctrine of allergy has found its warmest supporters among rhinologists. One example of this is the Dutch school of Benjamins. Directly in line with hay fever we may place occupational allergies, as in bakers, leather-workers, persons charged with the care of animals, hyper-sensitiveness to dust in nurses and to cosmetic powder in hairdressers etc. In these affections, too, the allergen is unmistakably recognizable as the morbid agent. Again, some skin affections and nutritional disorders may be attributed to the action of well-known allergens.

In all these patients, the connection between the disease and a specific allergen is undeniable; in fact, the correspondence to the anaphylactic experiment is practically perfect. It is not surprising, therefore, that it was considered justifiable to generalize this observation, and that such causative allergens were searched for also in other patients, suffering from asthma and other allergic diseases. Now the skin tests were expected to 'do their bit' in tracking down the unknown allergen. That, after all, was the necessary condition, either for the elimination of the allergen from the patient's milieu, or for desensitizing the patient to the allergen

In this way the expectation was aroused that, by investigating specific sensitizations by means of skin-testing, the problem of asthma and vasomotor rhinitis might, to a large extent, be solved.

Disillusions were bound to be frequent; for such a success could be completely achieved only in a limited number of patients. For a much

and who failed to react to the introduction of pollen into the nose—in about one per cent of cases, a positive skin reaction to pollen. Nevertheless, some of them had a relatively low dermal threshold and, in correspondence therewith, a high reagin content of the blood. This proves that there must be other factors, apart from the presence of reagins, if an allergy is to be rendered manifest.

Piness and Miller found that, among the allergic patients that reacted to pollen, only half had any hay fever trouble. The other half, therefore, must be classed as cases of either latent allergy, or para-allergy.

In common with Roux, we found that bakers who were hypersensitive to flour showed such para-allergic positive pollen-reactions in about half of the cases, while there was only an isolated case of typical hay-fever during the season. This is a considerably higher incidence than that of positive pollen reactions in other allergies One is naturally inclined to explain this curious association of flour- and pollen-hypersensitivity by assuming a chemical similarity between the allergens. This is known to exist between the grasses mutually; but, although the different brands of flour also belong to the graminaceous plants, they differ from the grasses in an allergic respect. For this reason we only rarely find the contrary case, namely, a positive reaction to flour among hay fever patients.

All the same, we are inclined to assume that this association of flour- and pollen-allergy is not merely accidental, and that their kinship becomes manifest in the form of a predisposing factor. That is to say, that the patient who is hypersensitive to flour is disposed to be also hypersensitive to pollen, and conversely. This disposition, however, will not *become manifest unless and until the exposure to the allergen in question* is sufficient. Now the exposure to pollen of the man who works with flour is normally present; hence the high percentage of manifestly positive reactions. The exposure of the hay fever patient to flour, on the contrary, is usually extremely slight; hence the small number of manifest reactions. But when a hay fever sufferer becomes a baker, he should, according to this theory, very soon develop a sensitivity to flour. Now this is, in fact, the case. Thus, out of some hundreds of bakers, we have never found a positive pollen-reaction without a simultaneous positive flour-reaction.

Next to the changeability of the results of the skin reactions, the equally haphazard occurrence of the attacks is also a cause of a great deal of misconception concerning allergy. In contrast to the laboratory animal, which can be made anaphylactic at any time, and invariably reacts with an attack to a given amount of allergen, the human allergic constitution is to a large extent determined hereditarily, and the occurrence of an attack is in a high degree independent of the allergic dosage.

Opponents of allergology are able to report cases of patients with positive skin reactions to a certain allergen, but in whom exposure to this allergen sometimes produces a reaction, and sometimes not at all.

Constitution, disposition, and exposure are the three pillars that support our understanding of the occurrence of attacks. The allergic constitution causes children of allergic parents to get allergic affections at an earlier age, and in greater numbers. The disposition determines whether, at a given constitution and exposure to allergen, an attack will, or will not, occur. This disposition comprises somatic, psychic, and local factors, which together determine the tolerance threshold of the autonomous nervous system. With respect to the somatic factors, one should think particularly of hormones and of infection, and with respect to the local factors, first and foremost of reflex-hypersensitivity.

Exposure to the allergen is the third condition, both for the genesis of an allergic affection, and for the occurrence of attacks. This factor is no less important than constitution and disposition. The occupational allergies have taught us that any group of the population may at any time be sensitized, up to a high incidence, by an intensive exposure to a potent allergen. Thus, bakers in small, badly ventilated bakeries proved to be sensitized to as high as 40 per cent., and in the large, well ventilated ones to 25 per cent. The percentage of sensitized workers was found to increase parallel with the number of years of service, so that we may well ask ourselves whether, given sufficiently long and intensive exposure, every person might not be susceptible to sensitization. In that case, a positive hereditary taint could only become manifest through an earlier occurrence of the allergic disease.

The doctrine of specific sensitization is now, once again, finding its opponents—this time, in the ranks of the psychosomatic therapists. They deny the importance of specific sensitization, on the ground of the desultoriness of the skin reactions and of the allergen as a morbific agent As against this, they hold that the cause of allergic diseases must be sought in psychic conflict situations. They point to the neurotic disposition of asthma patients, to their suggestibility during the occurrence of and the recovery from attacks, and to the results obtained by their treatment They deny, therefore, that, in man, anaphylactic processes play an important part.

No allergist would ever deny the great importance of the psyche in a human allergic disposition. Conditioned reflexes and associations are powerful factors in the occurrence of these diseases. The familiar examples described by Osler and Morell Mackenzie, such as asthma on looking at artificial flowers, and hay fever on looking at a painting, are readily supplemented by any allergist from his own experience The

same mechanism is equally well-known with regard to seasickness and gastro-intestinal disorders.

But it would be going too far to deny the unmistakably close correspondence between the animal experiment and human allergy. And it would definitely be going too far to attribute neurotic tendencies to entire groups of the population, such as hay fever patients, bakers and others who might be exposed to allergens.

The implication of such a theory would be that 40 per cent of people are neurotic, since—according to Vaughan—this is the percentage showing allergic symptoms at some time of their life.

As against this, too little attention has been given to somato-psychics, that is, the mental digestion of the fact of being bodily ill. Is it surprising that an asthmatic child seeks help for his distress, in his feelings of suffocation, with his mother, and that he may develop an ambivalent attachment to her? Surely adaptation to the presence of disease is quite as difficult in the case of asthma, as in deafness, infantile paralysis, or disequilibrium. Those suffering from acquired diseases of this kind show considerable resemblance with asthma patients; but nobody would wish to assert that they had a neurotic constitution before they fell ill. Neither can it be maintained that an excessively large number of allergic affections is found among evidently neurotic patients.

When we reflect upon the controversies which I have discussed, we find ourselves faced with the task of giving a reasonable evaluation of many different factors, and a justifiable description of their interplay. Skin reactions have their value; but the allergist should beware of arousing unfulfillable expectations. In the pathogenesis of allergic diseases a large number of—partly unknown—factors play a part. There are unmistakably somatic factors such as allergens, hormones and infections; but there are equally unmistakable psychic factors, such as existing conflict situations, conditioned reflexes, and the mental digestion of bodily distress.

We cannot help, therefore, being forced to look upon the allergic syndrome, not as either somatic or psychic, but as both somatic and psychic. This line of thought will come easier to the thinker trained in the philosophy of Hegel, than for him who prefers to adhere to the Kantian laws.

For the understanding and the treatment of such complex diseases, therefore, the allergist needs to possess a great flexibility of thought. No longer can he afford to be the skin-scratcher of former days; he will have to master the vast field of specialized allergological knowledge. This, however, is not enough; for he must also have a fully adequate knowledge of internal medicine. Only in this way is it possible to obviate diagnostic mistakes. And even then, he is not completely equipped for his work, for he will also have to study his patient's psychic condition.

That the awareness of these desiderata is not new or foreign to us will be clear to anyone who has made himself acquainted with the program of the adresses for the next three days. During these three days, both the asthma specialists and representatives of other branches of medicine will give proof of the measure in which the doctrine of allergology, in all its facets, and as an independent specialism, a basal science and an auxiliary science, is a living part of their professional study and deep concern.

But apart from knowledge, great zeal and high accuracy, the allergist must have a warm human heart. He must be able to cope with disappointments, and to impart courage and consolation, over and over again, to these patients who need his moral sustenance more than others.

ON THE HISTORY OF BRONCHIAL ASTHMA *

by

TH. H. SCHLICHTING

An attack of bronchial asthma makes an enormous impression, and one cannot wonder, that it has been mentioned already among the first medical accounts. In fact, bronchial asthma is mentioned in the Hippocratic collection, sometime between 500 and 300 C.

The description is rather accurate, since the expiratory dyspnoea has been noticed and laid down in script.

Now, a modern physician expects, that the Greeks would make haste to distinguish between this and cardial asthma, bronchitis and similar affections. But this was not the case. Their idea of the composition and structure of the body was so extremely simple, that they could not conceive a great number of different diseases to be possible. In their therapeutic measures they took their clue from the general condition of the body, and they did not care much about localization and specificity. This was the prevailing view and this state of affairs remained unshaken, as long as the Greek philosophy of nature, and notably that of Aristoteles, did prevail.

I have named the word specificity. This is a rather modern idea; its history may be said to begin with Paracelsus, it was unknown with the Greeks.

Celsus, in the first century of our aera, says: 'There is a disease situated in the regions of the throat, which causes difficulty of breathing When this disease is not too strong and thus not causes suffocation, it is called dyspnoea; when this disease is stronger and also causes noises and cough, it is called asthma; when it is still stronger, so that the patient can only breath with the neck extended, it is called orthopnoea.'

Thus all these affections are considered as one disease, in different grades of strength.

The first full-length description of bronchial asthma has been written by Aretaeus of Cappadocia, probably in the first half of the second century.

As to the causes of illness, the Greeks thought that they were either a shortage, or an excess, or a wrong quality of one of the four liquids, the four humours that is, of the body, and they directed their therapy to the re-establishing of the harmony between these four: blood, phlegm, white gall and black gall.

You can express their pathology in terms of these humours, but

* Lecture held at the Opening Ceremony.

you can do the same in terms of the four qualities, viz. heat, cold, moisture and dryness; because each humour represents a mixture of two qualities, and then you get four possible mixtures. As a matter of fact, this theory was not so bad, as it seems to us; they were able really to adapt their therapy to the different pathological states of the body. But there was another theory, preconized by Galen, that was far worse and, in reality, fantastical. It is the theory of catarrhs.

Galen imagined, but not for the first time, that gases rose from the lower parts of the body unto the brain, which was the cooler part; there the gases were condensated and from there flowed down and caused catarrhs—catarrhein means flowing down—of the nose, the eyes, the lungs etc.

The nature of bronchial asthma could be known only after the theory of catarrhs was discarded, after the destruction of the theory of humours, and not before same idea of specificity had been conceived and constructed.

The modern idea of specificity was in medicine unknown during the Middle Ages. In the footsteps of the Ancients people said, that man was more real than a man, or that the species man was more real than the individual man. This kind of viewing nature did not allow them to appreciate individual differences, i e. did not allow them to conceive specificity in our modern sense. It comes to the fore for the first time in the writings of Paracelsus and becomes strong in the following times.

The theory of catarrhs was not so very popular in the Middle Ages. To be certain of this, I have consulted an edition of Avicenna, who was from the 13th century in medieval eyes the greatest master of medicine, an edition annotated by Jacques Despars, a Belgian from Doornik, who was a professor at the Sorbonne about 1450, and whose annotations were six times as voluminous as the proper text of Avicenna. This professor knew all about medieval medicine—he was, besides, a great benefactor of his University—and he does not mention catarrhs in his writings about asthma. The catarrhal theory was revivified in the Renascence, as when people had an exaggerated reverence for Galen. Jacques Despars treats asthmatic conditions in the same way as he treats other diseases, that are caused by superfluous humours.

So this is the official theory. But you never know. In 1552 Geronimo Cardano was asked to cure Archbishop John Hamilton of Edinburgh. [illegible]

[illegible] knew, if I may say so, allergy, and he knew the role of the nasal mucosa. He cured the archbishop.

Practice, it is clear, is richer than theory. Clinical theory, indeed, did not grow in the 16th century, which was the century of anatomy. The 17th was the century of physiology. But the findings of anatomists and physiologists had only few clinical consequences. This is because there is a kind of historical law, which says, that a clinical theory does not disappear, as soon as its fundaments are destructed, but only, when another theory is able to take its place. Thus the clinical theory of Galen held good, while on the one hand its humoral theory was disbelieved, but at the other hand no plausible theory was available.

The first new clinical theory was that of the chemical theory of life, but in Paracelsus and Van Helmont it was combined with a strong vitalism. Paracelsus, as a matter of fact, did not quite disbelieve in the humoral theory, but Van Helmont, in the first half of the 17th century, attacked this theory furiously, and in particular the theory of catarrhs. He showed with many arguments and a few observations, that this theory is impossible and absurd. Also he gave same clinical histories, that are very rich in content.

1) A mayor of a big city falls on the head and the shoulders; he gets unconscious, he awakes, and he feels himself very well during the next eight months. After these months, he has some attacks of asthma. In the night he is sleepless and disturbed; his mouth is dry, he has a little fever, an enormous micturition, and about three stools; in the morning the respiration, like a thread, is cut off, and he suffers from a terrible orthopnoea. The attack ends with a manifest bronchial secretion. After a few days, he is completely restored.

2) A healthy sportsman, 24 years old, suffers his first attack, when he comes to visit Brussels; the attack takes three days. He gets home but cannot sleep but in a sitting posture. When he lays down, he has a beginning of asthma, but not a real attack. Some days are bad, but in the intervening days he walks and goes hunting. High places are the worst, and so he avoids Brussels.

3) A canon has asthma in summertime, no asthma in winter. When he has asthma, he has itchings, an enormous white desquamation of the skin, and he looks like a leper. His mother had the same itchings, and his sister too. But the latter was healed after the second childbirth.

4) A Franciscian monk has the duty of cleaning the house. Every time a little dust is raised, the monk is nearly suffocated. Also: he can not carry fried fish, and he gets an attack of asthma. Also: he has certain forebodings of asthma, just like the hunting man.

5) A hearty and modest citizen is publicly insulted by a magistrate; but he dares not answer from fear of utterly ruin. So he is silent, but

soon after he is visited by asthma, which grows in intensity. After two years he develops a moderate dropsy and he dies

Thus Van Helmont, who calls asthma epilepsy of the lungs, describes emotional asthma, allergic asthma from dust and food, and climate. Also he has a theory about the origin of asthma, but a vague and wrong one, and I shall be silent about it.

His writings about asthma date from about 1630

Now, in 1628 William Harvey published his celebrated book on the circulation of the blood, and out of this discovery came a strong argument against the catarrhal theory, because in 1659 Victor Schneider, in his big book on catarrhs, endeavoured to show that the catarrhal secretion did not come from the brain, but from the bloodvessels in the affected spot. About 5 years later Niels Stensen, the discoverer of the ductus Stenonianus, contended that the catarrhal secretion did not flow immediately from the bloodvessels, but from the mucous glands, which were discovered and described by him. Thus the whole fundament of the catarrhal theory was destroyed, first by Van Helmont with arguments, then by Stensen with facts.

Van Helmont was an iatrochemist, his school tried to explain physiology through chemistry, but another school which rose in the same time tried to explain physiology through mechanics, and since mechanics was at the time the best developed science, iatromechanics generally met with better success than iatrochemistry. And thus we hear at the same time a mechanical explanation of asthma, out of the brain of Willis, he considered spasm of the bronchioli as the cause of bronchial asthma

This is a very nice idea. But the great Sydenham did not like mechanical explanations, and in this case he did not deepen the knowledge of asthma.

A rather modern account was given by Sir John Floyer in 1698, but in the next century there was no great advance in the knowledge of asthma. The reason is, I think, that experimental science did not flourish in this century, people liked deductive science, i.e. explaining all things through one or two simple principles. And so asthma is, according to one school, nothing but enhanced irritability, and according to another, abnormal incitability, and to still another, an expression of an excessive nervous activity and so on

The 18th century was the century of rationalism

In the beginning of the 19th century a new school of medical thinking and investigating was founded by some Frenchmen, notably Bichat, Laennec and Corvisart.

In the previous centuries it had been proven, and foremost in the great work of Morgagni, that clinical diagnosis most often did not

coincide with post-mortem findings. The above named Frenchmen thought that the reason of this clash between clinical diagnoses and post-mortem findings was in that during life anatomical diagnoses should have been made, whereas in reality clinical, i.e. non-anatomical diagnoses were made. They were not contented with a clinical diagnosis v.g. chronic pain in the belly with stranguria, but they tried to make anatomical diagnoses during life, they developed percussion and auscultation. Laennec described for the first time many diseases of the lungs, and also of the liver. This is a well known fact in medical history, but at the other hand their whole way of thinking tended to the assumption, that anatomical diagnoses are the only real ones. So we find in the 19th century many more or less anatomical concepts of bronchial asthma

Of course, the outstanding theory, already more than a century old, was a neurological one. And this theory crystallized into the widely accepted thesis, that bronchial asthma was caused by a cramp of the small and smallest bronchial muscles. It sounded very simple and sufficient, and it got a thorough exposition by Biermer, the man of pernicious anaemia.

Before expounding this theory, we have to retain, that bronchial *asthma was, in the first half of the 19th century, conclusively separated* from cardial asthma, or oedema of the lungs, from emphysema and many other diseases This kind of clinical science was the great harvest of the anatomical school, and thus the site was prepared for the building of an etiological theory of asthma.

After many attempts by Longet and other people, Paul Best, a disciple of Claude Bernard, elicited an attack of bronchial asthma by stimulating the vagus nerve; the attack consisted in a tonical spasm of the bronchial muscles. Further, Biermer was satisfied, that the prolonged expiration and the sibili had to be explained through the bronchial spasm. This spasm caused an acute emphysema of the lungs, and this emphysema caused the depression of the diaphragma.

But why is expiration more difficult than inspiration, although the pression of expiration is stronger than the pression of inspiration? According to Biermer, this is because the strong pression of expiration compresses also the bronchioli, so that expiration is made more difficult; and furthermore it is a fact, he says, that in capillary bronchitis the expiration is not strong enough to extrude the mucus and so gives way to emphysema, while all the time inspiration is perfectly possible. This fact serves as an explanation of the greater difficulty of expiration.

Biermer cannot explain, why the attack of asthma ends with catarrhal phenomena. In his theory there is no place for secretion. But about this I shall have to say a few words later on.

Now this theory of Paul Bert and Biermer is, to a certain extent, a physiological one. But there were also anatomical theories of asthma in the 19th century; in the second half so called physio-pathological theories were en vogue

In this case, the anatomical theory of Wintrich was of a later date than the physiological one of Biermer.

Wintrich saw the origin of bronchial asthma in a tonical depression of the diaphragma; against Biermer he contended that bronchial asthma would have as an effect a relaxation, not a depression of the diaphragma; in fact, in asthma the volume of the thorax is diminished, the intercostal spaces are drawn in, and it is only natural that the diaphragma should be relaxed. So Wintrich drew from the depression of the diaphragm all phenomena of an asthmatic attack. His explanation had all the charm of the simple and obvious.

These was a third theory, which had also a great charm. Weber contended that bronchial asthma was due to the swelling of the mucosa; he saw an analogon of asthma in the swelling of the nasal mucosa; this theory was compatible with the role of the nervous system in asthma, because one could explain fluently the swelling of the mucosa by the excitation of the nerve supply of the bloodvessels. Weber had no difficulty in explaining the secretions and the catarrhal phenomena in asthma. And there were experiments made by a certain Lovén, who was able to induce hyperaemia of the mucosa by excitation of sensory nerves, and so he imitated the originating of reflectory asthma.

This theory has been consolidated by many considerations and it has many advantages indeed. But like the other theories it suffers from the disadvantage, that an enormous and cohering complex of symptoms is explained by one single cause, which is in itself of an haphazard nature. And one feels, on the rebound, a little sympathy for ways of explanation such as of Van Helmont, who thinks that a whole complex of ponderous physiological factors is disturbed and thus causes bronchial asthma, which is in itself of a disturbing nature. Perhaps I had better say, that the physiology of respiration was still thought to be very simple. At the present time, after fifty or sixty years, the 19th century theories retain not a little of their value, but modern theories of pathogenesis draw the attention to the reaction of the whole organism to a disturbance. This way of viewing disease has been fruitful in neurology, mainly, it seems, through the work of Kurt Goldstein and Von Monakow. I do not know, whether it has been fruitful in the case of bronchial asthma.

When, in the footsteps of Laín Entralgo, we call the theory of Wintrich anatomical, that of Biermer physiological, that of Goldstein biological, than the next step in viewing disease may be called anthropological,

or psychosomatic. This way is opened by the theories of Freud, and so bronchial asthma has been viewed as a symbolical disease.

Not only specialists, but also general practitioners, like myself, have seen cases of bronchial asthma, which were symbolical expression of internal emotion, for the most part, I think, of indignation and powerless anger. This view enriches our knowledge, and to a certain extent, also our understanding; our knowledge, because emotional asthma was rather forgotten and was certainly not rightly appreciated; it enriches our understanding to a certain extent only, because the so-called relation between body and soul has not become clear and diaphanous, but only better appreciated; and the nature of symbolical expression is better understood. It remains that the whole affair is very difficult, and certainly not to be expressed only in terms of anatomy and physiology. At the other hand, the anatomical and physiological problems *have not been superseded by the psychological view; but they are not* the sole problems, and it becomes very clear, that they are *part* of the life problem.

But we can safely say, that the psychological view has a great therapeutic value, because, in order to cure a patient, it is not necessary to understand his disease in its entire essence In former times, medical men have cured many diseases, while floating in clouds of ignorance. And this state of affairs will remain, I think, a few years longer. Understanding of asthma has grown in the 19th and 20th century; the problems have become more difficult, became more extended, but at the other hand, the investigator has got more facts. It seems to me, however, that the constitution of the asthmatic patient has not received enough attention; medical science has forgotten constitution and temperament since 1800. It is to be expected that understanding of bronchial asthma will be deepened by the new kind of pathogeny, which is the fundament of the theory of stress, as laid down by Selye and others, but this question is not yet a historical one.

Therapy always follows the theory of pathogenesis. When asthma was considered as brought about by superfluous humours, derivation and purgation were the logical remedies. When the cause was plethora, bloodletting was the means of healing; and as a matter of fact, Van Helmont and Sydenham advocated bloodletting. Now, extensive blood-*letting is practically a kind of hibernation, and one should not wonder,* that many cases are healed in this way. In the 19th century the idea of specificity grows enormously, and everyone looks for specific remedies; the now well known remedies were in the beginning often regarded as being specific. With endocrinology a powerful agent has been discovered: adrenalin or suprarenin. But right through the big stream of reigning theories are the cross-currents of emperical knowledge.

Strammonium and other such agents are discovered in this way. And in the school of so-called nature healing diet, water cures and gymnastics are applied.

But as the exposition will show you all kinds of therapeutic measures. I need not enlarge upon therapy.

I may conclude with the expression of the hope that you shall draw, both from theoretical and emperical knowledge, many old and new means of curing asthmatic patients, and I thank you for your gracious attention.

THE SOCIAL SIGNIFICANCE OF BRONCHIAL ASTHMA *

by

P. MUNTENDAM

Summary

The treatment of the sick, the fight against disease, and the social therapy can only be organized consciously and effectually providing the social etiology is known, and the social diagnosis has been determined; in addition to which the social prognosis must be included in the subject of study. In former times the organized fight against disease, and the social care of the people's health was still insufficiently based on the results of socio-medical investigation.

History

In antiquity, it was especially Hippocrates who attached importance to climatological factors in the genesis of asthma; Galenus sought an explanation of asthma from the angle of humoral pathology. Maimonides, towards the end of the Middle Ages, points to the asthma patient's hypersensitivity to certain substances, and this is confirmed in the 18th century by William Cullen. Meanwhile, as early as the 17th century, the hereditary tendency to asthma had been pointed out, while the bronchial spasm—which, too, had already been discovered by that time—was confirmed by the development of 19th century physical diagnostics. New concepts, allergy and anaphylaxis, begin to occupy medical thought, while the psychogenic factors and their proximate causative action call for increasingly serious attention.

Definition of the concept

The definition of the concept 'asthma' may differ according to the views held with respect to the genesis of the disease. The attacks of bronchial constriction constitute the nucleus of all such definitions.

Social etiology

In close connexion with the etiology of individual cases, we should bear in mind the influence of the patient's milieu; causes which either act through physical, mechanical, chemical or biochemical factors, or should be ragarded as mental and/or social milieu-influences. Among the first group, the patient's housing, the factory or workshop, the climate, his

* Lecture held at the Opening Ceremony. Dr. P Muntendam, professor in the University of Leyden (Holland) is Director General of Public Health

diet, and further, animals, plants and micro-organisms may play a part. The mental milieu is especially determined by the atmosphere prevailing at home and at work; the social milieu depends, among other things, on the patient's economic circumstances

This part of our study includes also genetics. It is generally assumed that the heredity of an allergic constitution is irregularly dominant. It is this constitution which determines the individual's asthmatic reaction, either to a psychic conflict, or to the action of an allergen

Social pathology

The significance of the disease for society (social pathology) constitutes its social significance in a restricted sense.

Morbidity. According to the records of the 'Centraal Beheer' (i.e. Netherlands Central Administration Office of Social Insurance) the number of cases of asthma per 100 workers, in 1937, was 0.10 per cent, and in 1953, 0.36 per cent. This would mean that, out of the total population of the Netherlands, 36,000 persons were absent from their jobs in 1953 on account of asthma. The increase of the number of asthma cases is the more evident when we find that the total number of cases of all diseases was, in 1953, only double that of 1937 Further, other diseases in which a psychogenic cause may be assumed, also increased considerably in the Netherlands after the war, so that the rise in the incidence of asthma also points in the direction of the psychic factor in the genesis of the disease.

From two different investigations (Orie at Groningen, and Groen with the Philips concern, Eindhoven) it appears that the total number of asthma patients in the Netherlands is greater than the number of absentee workers. Both these investigations show between 1 and 1.5 per cent of the population, which would amount to about 100,000 asthma patients in the Netherlands.

There exist no clear and reliable data concerning the spread of the disease in this country. But what does strike one is the fact that the number of men rejected for military service on account of asthma is invariably and considerably lower in the southern provinces (Limburg, N Brabant) than the national average, while the north-western province (North Holland) is constantly far above the latter average.

The investigation in school-children, held last year, showed that morbidity among these children was about equal to that among adults, viz ± 1 per cent.

It is already clear from the above data that, *in the Netherlands asthma is of very great social significance.*

According to the data published by Unger, showing that 60 per cent of asthma patients are between 20 and 40 years of age, this means that, in

the Netherlands, there are about 60,000 asthma patients in the age-classes of productive workers.

Course of the disease. The *mortality rate* due to asthma is not very high in the Netherlands. In 1950 it was (standardized), for men, 6.1 per 100,000 inhabitants, which is slightly below the asthma mortality in Britain (Williams: 7.1 per 100,000 inhabitants in the years 1930–1948). For women, the death rate was lower, viz. 4.4 per 100,000 inhabitants. The asthma mortality figures, however, have trebled in the Netherlands since 1920; but closer analysis will be needed to show whether this increase is in accordance with reality. Notwithstanding the relatively low mortality, physicians examining persons for a life insurance are somewhat hesitant in accepting asthmatic candidates, in view of possible complications or other affections based on an allergic constitution.

Although the *duration*, per case, fell from 30.4 days in 1937 to 24.5 days in 1950, the total number of working days missed on account of asthma was nearly trebled. Possible explanations of this may be the intensification of psychic factors as morbific cause after the war, and the increased employment of older people among the working population.

Invalidity The age-spread of those in receipt of invalidity benefit on account of asthma, from the 'R.V.B.' (i.e. Netherlands State Insurance Bank) was, in 1952 and 1953, as follows:

17–20 years	2	40–50 years	214
20–30 „	69	50–60 „	251
30–40 „	109	60–65 „	103
		65 and older	17

This total of 765 National Insurance annuities amounts to 2.3 per cent of the total invalidity benefits paid out. The total amount paid out on account of asthma was *f* 94,546 68 (68 = cents). On January 1, 1955, 610 of these annuities were still running, 79 being terminated due to patients' recovery, and 76 owing to death.

The percentage of invalidity annuities paid to women on account of asthma, out of the total amount of annuities paid to women, shows a rising curve, i.e. from 0.6 per cent in 1948 and 0.5 per cent in 1951, to 2.2 per cent in 1953. This too may perhaps be explained by the employment of an increasing number of older women, and increasing psychic tensions in connexion with the ever rising industrial productivity.

Social and economic significance. The total amount of sick-pay received by asthma patients from the Central Administration Office of Social Insurance was, in 1937, just over *f* 20,000.— and in 1950 nearly *f* 181,000.—; viz over 1 per cent of the total amount of sickness benefit paid out. Out of a National Insurance Fund covering 200,000 insured

persons, an average of 74 patients per year were admitted to hospital, at a cost of about *f* 30,000 —. This would amount to more than 1 million guilders for the total number of persons insured with a sick-fund in the Netherlands, for the hospitalization of asthma patients alone

With regard to the non-insured section of the Dutch population we are unable to assess the socio-economic significance of disease; a fact which is to be regretted particularly with respect to married women and housewives.

The testing of a person for a given kind of job is a matter of considerable socio-medical significance, also in the case of asthma In addition to declaring a person unsuitable for certain trades (e.g in dusty surroundings) the test should also be directed positively, i e. towards such types of work as the asthma patient may safely be entrusted with.

Social therapy. The fight against any disease is closely bound up with its causes and its consequences for society, while the possibilities of exercising influence in both a prophylactic and curative sense should also be known. So long as this is not the case, it will be better to direct the available financial means towards scientific investigation, rather than towards the creation of a large and expensive organization.

The knowledge of the causal treatment of asthma justifies, next to supporting scientific investigation, also the creation of an organization devoted to fighting the disease. In this, especial attention should also be given to the psycho-somatic treatment of asthma (psychotherapeutic group therapy according to Groen), which has been more and more in the centre of interest in the Netherlands during recent years

Before all, however, the organized fight against asthma should be directed at *the child.* By taking heredity into consideration when giving pre-marital medical advice; in giving dietary advice to expectant mothers and during the breast-feeding period, and in creating a psychically and hygienically healthy milieu, powerful contributions can be made to the success of this fight. More especially, organized care of infants-in-arms and babies by the existing consultation bureaux, and their arrangements for district visiting, as well as medical supervision in the schools, will facilitate attention being given to the children's psychic milieu.

Most interesting are the results of the treatment in the 'Heideheuvel' Institution at Hilversum There, an extremely pure psychic milieu is created for the children; the feeling of 'being ill' is completely repelled; the therapy including the absence of any special anti-allergy diets. 'All the children join in eating everything". So far, the results are most gratifying. The children's non-attendance at school is below that of other Hilversum children. After 6 months, 73 per cent of the children were 'well', 23 per cent 'moderate, but improved', and 4 per cent

without improvement. To achieve a lasting result it is especially the simultaneous improvement of the family milieu, and the social after-care that are important if this physical and psychic sanitation is to be perpetuated.

For the organization of an early and effectual treatment of asthma in children, the following are imperative:

1) General guidance and education of the population into understanding that asthma is a disease which can be treated in such a way as to ensure for the child a full future life.

2) Individual guidance and instruction of the asthma patient's milieu.

3) Early recognition of symptoms through consultation bureaux for infants and babies, and medical supervision in schools.

4) Creation of scientific centres for investigation and therapeutic advice.

5) Foundation of therapeutic institutions.

6) Organization of after-care.

With regard to the fight against asthma in adult patients, those measures are of particular importance which are directed towards the improvement of the working milieu, both in a physical and chemical sense (Safety Act, Stonemasons' Act), and in a psychic-hygienic sense. In this connexion, great value must be attached to the establishment of industrial medical services, and the medical consulting hours in factories, which may make a considerable contribution to the relationships among the personnel in the industry. In addition, the enforcement of the Partially Unfit Workers Act (2 per cent partially unfit compulsory in large concerns) may be of importance for asthma patients

The implementation of the programme here developed demands the concern and the financial co-operation of the entire population. Admittedly, the Netherlands Budget since 1951 has included a modest item (for 1956 ca. ƒ 400,000.—); but both the Government's contribution and those of the general public towards private organizations remain insufficient for the fight against this socially important disease. For this reason, this opportunity was seized to stress the great significance, for both the people and the individual, of an efficient and successful fight against asthma.

ASTHMA IN A PARISIAN OUT-PATIENTS CONSULTATION*

by

B. N. HALPERN

The asthma problem in Paris is not very different from that in the Netherlands. But due to the great difference between climatic conditions in Northern and in Southern France the frequency, the causes and the complications of asthma are quite different in Lille and in Nice.

Paris is situated in the northern part of France and its climatic conditions are not very different from those in the Netherlands. The patients whose cases will be analyzed here come from our out-patients consultation of Prof. Vallery-Radot's clinic in Hospital Broussais Because the number of hospital beds available in the Parisian hospitals since the war is extremely limited, it became a necessity to study and treat asthma patients in an out-patients consultation which is similar to a physician's office. But unquestionnally there is a crying need for institutions for study and treatment of asthma, similar to those used in the treatment of tuberculosis Prolonged rest, a convenient diet, the choice of suitable climatic conditions, the psychological role of the nurses and physicians in whom the patient has confidence, the feeling that he is in specialized institutions, all this will comfort the patient and make the difficult task of the physician easier

Status asthmaticus cannot be treated satisfactorily in any place but in the hospital. Fortunately the incidence of patients in status is very low now. This leaves a great number of patients who are ambulatory and who can be studied thoroughly and satisfactorily in a well organized out-patients consultation. At the out-patients consultation of Prof. Vallery-Radot's clinic which is the only one really specialized allergy clinic, about 1000 – 1500 patients are seen every year mostly for asthma.

It is most important to explain to the patient, on his first visit, the nature of the disease with which he is affected. Hope of a cure should not be withheld. Asthma can be cured completely providing that the patient has not developed changes of irreversible type. If emphysema has occured, then our prognosis must be guarded and the patient should be relieved and the progress of the disease retarded, but a complete cure becomes highly problematic. We explain to the patient that no immediate miracle will be performed, and that satisfactory results can

* Lecture held at the Exposition.

only be obtained by full and absolute co-operation between the patient and the doctor and that the treatment must be carried out over a long period of time. If the patient is unwilling to co-operate on this basis, it is best for both physician and patient to part company then and there. Asthma is a discouraging disease from the viewpoint of the patient and a difficult one from the physician's viewpoint. Consequently asthmatics become notorious 'shoppers' (H. L. Rogers). They very often become unfaithful to their doctor for charlatans who are able to cure asthma by some miraculous magnetic fluids. An attempt should made to discourage this kind of behaviour.

Patients treated at the out-patients consultation come from two sources:

1) Those referred by outside physicians.
2) Those who are sent by other patients.

1) For the first group of patients, a complete report of the findings is sent to the referring physician. Often we are sending the necessary allergen-extracts to the physician with brief but definite directions for their use. The patient is re-adressed to me after the first month of treatment. This visit is very important. It is similar to the first visit to the garage of your new car after its running in. All symptoms are carefully discussed and a further effort is made to determine what produced them. It is important to check the reactions to the allergen injections in order to adjust the dosage.

The patient is then referred to his general practitioner with new instructions. The advantage of this plan is to build up a teamwork between the general practitioner, the patient and the specialist. Careful and diplomatic coaching by the specialist brings about intelligent co-operation on the part of the referring physician.

2) The patients who come direct to the clinic are treated in the hospital by some of the assistants under our supervision. The essential elements of the examination are:

History: the initial history is important. It is usually taken by the specialist himself, after a general examination by one of the senior students. We use history forms which are time saving and tend to a more orderly recording of the facts. They should not become too mechanical. The patients are requested to tell first their troubles and after that they are inquired about the following facts:

The age of onset.
The frequency and severity of the attacks.

The circumstances of the appearance of the attacks: at home, at work, by day, at night?

The influence of the season, of the climatic conditions.

The nature and amount of sputum.

The role of infection.

Has there ever been an attack brought on by the use of a drug such as aspirin?

The influence of dust or animal dander.

Has the patient vasomotor rhinitis?

Is the patient recovering his breath completely once the attack has passed? This gives an idea about the degree of emphysema

The inheritance factors.

Other allergic conditions which have preceded or are concommittant with the asthma.

If the patient is a woman, it is important to know the role of the menses.

What are the drugs which provide relief?

Is the patient using sympatho-mimetic drugs?

Is the patient taking any treatment between the drugs?

The physicial examination: The entire respiratory tract is given a thorough examination. We know that the upper respiratory ways are mostly participating in the allergic troubles and their physicial aspect gives a very definite idea of the state of the bronchial mucosa. A good asthmologue should be also a good rhinologist. It is therefore very important to note the aspect of the nasal mucous membrane and the state of the sinuses The nose should be examined for

Presence and aspect of discharge.

Color of the mucous membrane:

a) pallor and edema denote allergy.

b) smooth red congestive membrane usually denotes infection.

Presence of polypoid degeneration of the turbinates

Any malformation of the sept.

Transillumination of the sinus is a very simple procedure and should be routinely done. A great deal of informations can be gleaned from this examination.

If the sinus do not transilluminate clearly, this examination should be completed by x-rays study. The aspect of the postnasal pharynx is of interest The examination of the chest is of course of the greatest importance. The type of the chest should be noted and if there are symptoms in favour of emphysema, the diagnosis should be reserved. We should regularly measure the difference of the chest circumference in inspiration and in expiration with a tape measure. Spirometry is a routine-procedure.

The auscultation gives an idea of the respiratory type and shows the various rales. By the way I am noticing the presence of humid rales on the bases of the lungs, indicating a heart congestion. The condition of the heart is of the greatest importance.

The presence of an enlarged liver, of peripheral edema, cyanosis must be noted. Radioscopy and radiography or tomography are routinely applied.

The last part of our examination are the skin allergic tests. Scratch tests are the usual procedure with exception of house dust, moulds and food allergens for which intradermal testing is applied.

When the patient has been tested, one should keep in mind that severe general reactions may occur and that the physician should always have at his disposal adrenalin and phenergan.

The following allergens are usually tested:

House dust Endo 1/4000 1/400.

Moulds. Cladosporium, Alternaria, Penicillium: 1/100 solution.

Feathers.

Danders: cat, dog, horse, cattle, goat hair.

Orris root.

Cereals.

Orchard and timothy grass

Milk, egg, cereals, celeri, tomato, spinach, some meats.

The results of the testing should of course be set side by side with the clinical facts.

In our country it is possible to find an allergic cause of asthma in 60–70 per cent of the patients whose asthma started before the age of 30. The percentage of positive reactions decreases abruptly when asthma starts after the age of 40–50.

TREATMENT

The problem of the treatment should be considered under two different angles: treatment of the attack and the basic treatment.

a) *Treatment of the attack*

Adrenalin should be used with caution We are convinced that a too extensive use of adrenalin leads progressively to abuse and aggravates the asthma. Many of our patients came to a severe state of status asthmaticus by abuse of sympatho-mimetic substances. What is true for adrenalin is also true for aleudrine.

Theophyllin injected by intravenous route can stop a moderate asthma attack. We use a solution containing 250 mgm. per 10 ml. Aminophyllin should be injected slowly. It can be repeated twice or three times daily. It can be also administered by intramuscular way or rectally.

Morphine should never be administered in status asthmaticus. Morphine is responsible of many deaths. In severe cases of status asthmaticus we are using now either cortrophine or cortisone. For ambulatory treatment we use ACTH by intramuscular route while, in hospitalized patients, intravenous drip is prefered.

Blood lettings are sometimes efficient.

Pyrethotherapy is sometimes used when hormones are contra-indicated.

At our out-patients consultation we have an *aerosol-room* and very often an aerosol treatment is efficient enough to arrest an asthma attack. We are using almost exclusively theophyllin.

b) *Basic treatment*

*The problem is quite simple for those patients who are allergic to a well-*known allergen The desensitization treatment which is now applied in many thousands of patients gives generally excellent results. In Paris, 50 per cent of our patients suffering from rhinitis or asthma are treated in this manner We have about 100 per cent of success in pollinosis and near to 90 per cent in dust and moulds allergy.

The pharmacotherapy of these patients must be eclectic and cannot be uniform. Some of our patients are using hormones since 3–4 years with a satisfactory state. We are using either cortisone 50–100 mgm. a day or hydrocortisone 30–40 mgm. a day, or ACTH. The usual Na restrictive diet supplemented with Potassium is applied. Theophyllin is one of the most valuable drugs in treatment of asthma particularly when given rectally or parenterally. Many associations of theophyllin with coffeine, ephedrine, phenobarbital, iodides exist in France and are largely used

Theophylline is also very often used in form of aerosols. This kind of administration is used now not only by the specialist and in the hospitals but by almost every practitioner. It is harmless and gives very good results not only in acute state but also in maintenance treatment. It is interesting to note that the repetition of aerosol treatments can provide a long lasting relief.

Antihistaminics are usually efficient in allergic rhinitis. In asthma the results are confusing and irregular. We have been able to show that antihistaminics and especially phenergan are regularly active in the prophylactic treatment of asthma which is produced by high molecular proteins, such as danders, feathers, animal proteins. In asthma produced by small molecular allergens, such as dust, moulds allergen and even pollen allergen, antihistaminics are not very helpful

It is difficult to explain the difference of action in the two groups of patients. Antihistaminics are almost completely inactive in infections

and in non proteinic asthma. Our bronchoscopic studies indicate that in these cases local or regional spasm produced by irritation by the modified secretions is responsible for the dyspnoea. Theophyllin, iodides, ephedrin and hormones are much more helpful in these cases.

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PROBLEMS AND POSSIBILITIES FOR THE GENERAL PRACTIONER DURING THE TREATMENT OF BRONCHIAL ASTHMA*

by

A. H. VAN LIDTH DE JEUDE

Summary

I would first briefly mention the general practitioner's difficulties in treating persistent cases of bronchial asthma, because of the feeling of disappointment and annoyance on the part of both patient and physician, which further jeopardizes any still remaining chances of successful outcome of the treatment. I here distinguish between 'difficult' and 'troublesome' cases; and I suggest that, instead of resigning himself to the fact or the possibility that a disappointed patient may seek help elsewhere—usually with equally unsuccessful result—, the doctor should endeavour to find out whether there may not be certain factors in the circumstances of the patient's personal life that may be responsible for the genesis and/or continuance of the affection, and which, if revealed and consciously realized, may open up a new outlook suggesting different therapeutic measures. I will now describe three case histories by way of illustration.

Case 1. Man, aged 49, married, with one daughter. Has attacks of asthma when at home (week-ends) with his wife and child, but never when away during the week. Was treated in many different ways, without lasting success A private conversation revealed that he had been initiated into the 'facts of life' when a boy of 16, by a widow, the mother of a school friend. He later married, but his wife was cool towards him, and their sexual life was unsatisfactory. After many years of unsuccessful treatment, the long, confidential talk with the doctor led to a separation from his wife, after which the attacks gradually ceased.

Case 2. Woman, aged 32. Came for treatment in 1953, having had attacks for 7 years. Rather unhappy youth. Married in Zeeland after 4 years' courtship. Father-in-law indifferent; mother-in-law against the marriage. Husband also very callous towards her. Coitus very painful. Patient says: 'I need a lot of love; if anybody is kind to me it does more good than a hundred injections'. Repeated treatment by internists -

* Lecture held at the Exposition.

where P = force, V = dx/dt = velocity, Po = isometric tension, a and b are constants with the dimensions of a force and a velocity respectively. Arranging the equation in this form makes it clear that the force-velocity curve is part of a rectangular hyperbola. The form V = (Po − P) b/ (P + a) may be more evocative; for it shows that the velocity depends on the difference between the actual force acting on the muscle (P) and the maximum force which it could develop (Po).

Not only does Hill's equation fit the experimental force-velocity curves of many different types of muscle; but also one of its constants (a) can be determined independently from either mechanical or thermal measurements and the two estimates agree reasonably well.

It should be noted that since Po appears in it as a constant, Hill's equation can only be applied near the flat top of the tension-length curve, i.e. where the muscle has about its *in situ* length. Moreover, since the elastic component has been eliminated by recording isotonically, the equation applies to the contractile component alone.

Dynamic Performance with Various Types of Load

In the region of its *in situ* length, the mechanical behaviour of the tetanized whole muscle thus appears to be fully determined by the equation

$$V = (Po - P)b/(P + a) - d[f_1(P)]/dt$$

where $x = f_1(P)$ is the equation of the stress-strain curve, known experimentally from Figure 4. This makes it possible to predict how the muscle will react when it is confronted by any specified mechanical system.

Inserting the appropriate relationship (imposed by the external mechanical conditions) into the above equation, the following cases have been worked out:

1. Isometric contraction. V = O, therefore

$$(Po - P)b/(P + a) = d[f_1(P)]/dt$$

i.e. the rate of internal shortening of the contractile component = rate of internal lengthening of the elastic component. The

solution to this equation describes the way in which isometric tension rises with time. It is in good accord with experimental fact (Hill, 1938; Wilkie, 1950).

2. Imposed constant velocity (Levin-Wyman lever); $V = \text{const}$ (Hill, 1938).

3. Inertia wheel; $P = M\, dV/dt$ (Hill, 1940).

4. Inertia + constant force F; $P = F + M\, dV/dt$.

This last is the situation which confronts a muscle in the living body. The predicted result, which becomes oscillatory under certain conditions, is in good agreement with experimental findings (Wilkie, 1950).

Although it is easy enough to write down these differential equations, it is often impossible to solve them algebraically, because they are non-linear. The result must then be obtained by computational methods or, much more simply and quickly, by building an electrical analogue circuit (Wilkie, 1950). The contractile component is imitated by a battery in series with a non-linear resistor; the elastic component by a non-linear capacitance and the external load by appropriate inductances (= inertias) and batteries (= forces).

Twitch and Tetanus: the Active-state Curve

The physical state of a muscle is exactly the same during the early part of a twitch and during a tetanus (after all, the muscle cannot know after the first stimulus whether or not other stimuli are coming). However, the contracted state or 'active state' does not last very long; and after only one stimulus there is not time for the isometric tension or the isotonic shortening to reach its full (tetanic) value. The exact way in which the active state appears and disappears has been extensively studied in recent years, for there is abundant evidence that many drugs act by altering the time-course of this process.

Definition of active state. The intensity of the active state at any instant is defined as 'the isometric tension which the contractile component can develop (or just bear without lengthening) at that instant'. The tension in the whole muscle follows a much slower time-course because of the series elastic component.

(1) *The onset of activity* begins very soon after the stimulus. The

first change in mechanical properties (at 0°) can be detected after 3 m.sec. (Hill, 1951b); spontaneous tension development after about 12 m.sec. (Abbott and Ritchie, 1951); and isotonic *shortening* after about 20 m.sec. (Hill, 1951a). Since isotonic shortening begins at its full maximum speed, one may conclude that by this time the active state has already reached its full intensity.

(2) *The plateau of activity.* Activity remains at full intensity for an appreciable time after the stimulus (40 m sec. at 0° C., 10 m.sec. at 20° C.). During this period the muscle behaves exactly as though it had been tetanized (Macpherson and Wilkie, 1954). If the effect of the series elastic component is [illegible] 949) [illegible] the muscle can develop, or bear, the full tetanic tension.

(3) *The decline of activity.* The apparent duration of the plateau varies inversely with the sensitivity of the tension-recording apparatus employed. Thus if a piezo-electric crystal is used instead of a transducer valve, the first decline from the plateau can be detected at 34 m sec. (Ritchie, 1954a) instead of the 40 m.sec. quoted above. The falling phase of the active-state curve can be determined without this ambiguity by the method described by Ritchie (1954b). When the rate of change of tension in a muscle is zero, its elastic component must be at unchanging length. This occurs at the peak of an isometric twitch; and since the total muscle length and the length of the elastic component are then both unchanging, the contractile element must also then be neither lengthening nor shortening. In this situation, the tension which it exerts (which is the same as the tension exerted by the whole muscle) must be equal to the intensity of the active state, according to the definition given above. By releasing the muscle at various instants after the stimulus, Ritchie obtains a set of twitch-like tension records (Figure 7). The peak of each of them must lie on the active-state curve, which is thus indicated by the dashed line in Figure 7.

The apparatus is arranged as shown in Figure 7. The (unloaded) lever is prevented from moving by the stop, and is

attached to the transducer by a slack connexion. The amount of slack does not matter so long as it is greater than the amount by which the series elastic component is stretched at the height of contraction—that is, about 1·5 mm. (see Figure 4).

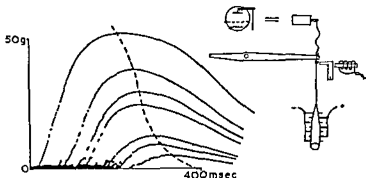


FIG. 7. The active-state curve Apparatus and experimental tension-time curves The dashed line drawn through their peaks shows the decline in intensity of the active state.

When the muscle is stimulated, it develops tension isometrically, but this is not recorded When the stop is suddenly removed, the series elastic component shortens abruptly (as in Figure 3) and the tension falls to zero. However, an active contractile component then redevelops tension, which is recorded as in Figure 7. The later the release, the less tension redevelops.

The active-state curve is very easily influenced. Its falling phase is delayed by adrenaline, caffeine (Goffart and Ritchie, 1952), nitrate, bromide, iodide (Hill and Macpherson, 1954), quinine (Lammers and Ritchie, 1955), certain quaternary ammonium salts (Ritchie and Wilkie, 1956), also by previous stimulation (Ritchie and Wilkie, 1955), decrease in temperature (Macpherson and Wilkie, 1954), or increase in hydrostatic pressure (Wilkie, 1954, unpublished). These effects are probably all mediated at the surface of the muscle fibres (Hill and Macpherson, 1954).

THE CHARACTERISTIC CURVES OF MUSCLE

In earlier sections the mechanical condition of active muscle has been specified by four curves:

(1) The stress-strain curve of the series elastic component. $x = f_1(P)$.

(2) The tension-length curve. $P_o = f_2(x)$.

(3) The force-velocity curve. $\frac{dx}{dt} = f_3(P)$.

(4) The active-state curve. $P_o = f_4(t)$.

P = force, P_o = isometric force, x = length, t = time, f_1, f_2, etc. are to be regarded purely as empirical functions defined by *the experimentally determined shapes of the curves.*

Curve (1) does not depend directly on the contractile machinery. Curves (2) and (3) seem to express the properties of the contractile proteins inside the muscle fibres. Similar curves are obtained from glycerol-extracted muscle fibres, activated by ATP; and even from artificial threads of muscle protein which has been in free solution (see e.g. Weber, 1954).

In contrast, curve (4) arises from the mechanism by which the contractile machinery is switched on and off in response to changes of potential at the cell membrane.

Each of the curves gives only a partial view of the active muscle, for each of them is made by holding all but two of the parameters constant and observing the relationship between the remaining pair. How should one combine the curves when all the parameters are varying at once, as they may do in an actual contraction?

Shortening and the tension-length curve. The force-velocity curve, $dx/dt = f_3(P)$ can be written in algebraic form (Hill's equation):

$$dx/dt = (P_o - P)b/(P + a)$$

Since P_o appears in it as a constant, this equation applies only for small length changes in the region near the flat top of the tension-length curve However, the equation can be modified to apply at other lengths by arranging that P_o should vary with muscle length according to the tension-length curve:

$$dx/dt = [f_2(x) - P]b/(P + a)$$

This equation describes the full range of shortening of the tetanized muscle with fair accuracy (Abbott and Wilkie, 1953).

Dynamics of a single twitch. Hill's equation can be modified also

to take account of the decline in activity following a simple stimulus by altering P_o both as a function of time and of length:

$$P_o(x,t) = f_3(x) \cdot f_4(t)/P_o^*$$

P_o^* is the original P_o of Hill's equation, i.e. the tetanic tension at body-length.

So the equation becomes

$$dx/dt = [f_3(x) \cdot f_4(t)/P_o^* - P]b/(P + a)$$

This equation can be tested by inserting experimentally determined values for P_o, a, b, and for the tension-length and active-state curves; then integrating to find how x changes with t for different values of P; i.e. one predicts the shapes of isotonic

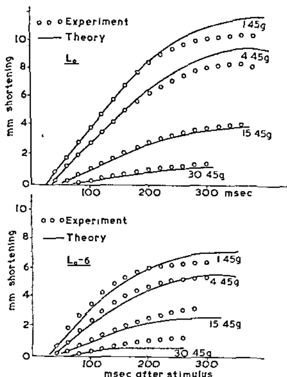


FIG. 8. Theoretical and experimental isotonic twitches.

twitches against various loads. This work (Ritchie and Wilkie, 1955–6) is still in progress. Results so far show fair accord between theory and experiment, as illustrated in Figure 8, where the equation is tested at two different initial lengths as well as

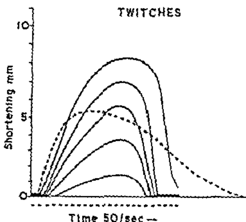


FIG. 9. Isotonic and isometric twitches superimposed on the same time scale. Isotonic tensions, from above downwards, 1, 2·5, 5, 10, 20 grams weight; peak isometric tension, 28 5 grams weight.

at several different loads. This equation may therefore be regarded tentatively as the general equation describing the mechanical properties of contracting muscle; from it the various characteristic curves emerge as special cases.

Relaxation. So far we have confined attention to the phase of contraction. The mechanical state of the muscle in the succeeding phase of relaxation is not well understood at present.

Figure 9 shows that relaxation is much slower under isometric than under isotonic conditions, leading to the apparent paradox that the muscle is able to sustain a given isometric tension long after it has been obliged to drop a weight producing the same tension. The explanation for this is not certain, but it may be that the muscle proteins retain some of their contracted structure until they are disrupted by forcible lengthening.

An examination of the mechanical properties of muscle along these lines should make possible a more penetrating analysis of the various factors which influence contraction. Many drugs

alter only the active-state curve; temperature change alters both the active-state curve and the force-velocity curve while the tension-length curve is more or less independent of external influences. The curves thus appear to reflect separately the properties of separable parts of the contractile machinery.

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XVIII

Proteins in Muscular Contraction

S. V. PERRY

To understand the role of the muscle proteins in contraction it is necessary to be able to describe the marked changes which occur in muscle tissue during activity in terms of the proteins themselves. Unfortunately we are not yet able to do this, but in recent years some progress towards this goal has been made and I wish in this lecture to relate our knowledge of the muscle proteins to the structure of the cell as a whole and in particular to those morphological components within the cell which are responsible for contraction.

The cytoplasm of cells from smooth, cardiac and skeletal muscle tissues contains large numbers of longitudinal structures known as myofibrils. These structures have long been recognized as the site of the contractile process and the study of muscle has been largely devoted to the study of the myofibril itself as a morphological unit, or to substances derived from it. Apart from the myofibrils the skeletal muscle cell contains the usual formed elements such as nuclei, glycogen, fat granules, endoplasmic reticulum and lipoprotein granules (the larger of which correspond to mitochondria and which are perhaps best

is now clear that they have indirect roles to play. In the mitochondria are localized the enzyme systems by means of which oxidative processes are harnessed to produce adenosinetriphosphate

(ATP), whereas the anaerobic production of this substance takes place in the soluble sarcoplasm where the enzymes of glycolysis are found. The relative importance of these two systems in providing the fuel for the contractile activity of the

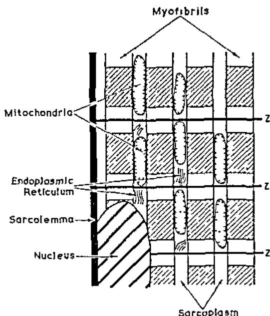


FIG. 1. Schematic representation of the skeletal muscle cell There is a wide variation in the number and size of the sarcosomes found in different skeletal muscle cells In the diagram the mitochondria are shown to be relatively abundant as in a highly oxidative tissue such as pigeon breast muscle In some mammalian muscles the sarcosomes are smaller and may be associated with the I band.

myofibril is reflected in the morphological appearance of the muscle. Tissues of high oxidative activity such as cardiac muscle and the wing muscles of insects and of birds contain numerous large mitochondria, whereas in the skeletal muscles of most mammals the mitochondria are much smaller and less abundant.

Since the fact that about 80 per cent of the dry weight of muscle consists of protein suggests that the contractile system is built up from this substance, it is not surprising that the muscle

proteins have been intensively investigated. From the work of a number of investigators (Halliburton, 1887; Von Furth, 1895, 1919; Weber, 1925, 1927; Weber and Meyer, 1933) it was apparent that two main protein fractions could be obtained from skeletal muscle tissue. The fraction obtained by extracting minced muscle with water or solutions of low ionic strength (<0·15) was known as the myogen fraction and was later found to contain all the enzymes necessary to convert glycogen into lactic acid. When the extraction was carried out at higher ionic strength (>0·5) large amounts of a globulin, myosin, which gave rather a viscous solution, was obtained in addition to the myogen fraction. It was presumed that myosin was derived from the myofibril—a view which has been amply confirmed by the study of isolated myofibrils. Also it is now realized that solutions of low ionic strength simply extract the soluble sarcoplasm, whereas to bring the proteins of the myofibril into solution higher salt concentrations are required to break down the forces which bind the protein components together in this structure.

Subsequent investigations of the myofibrillar protein fraction indicated that in addition to myosin two other proteins, namely actin (Straub, 1942, 1943; Szent-Györgyi, 1945) and tropomyosin (Bailey, 1946, 1948) were present. Any understanding of the role of these substances in contraction requires knowledge of their localization in the myofibril and consequently the discussion which follows will be primarily concerned with this aspect and with the interaction of the myofibril and ATP.

Structure of the Myofibril

The skeletal muscle myofibril at equilibrium length is characterized by two main bands—the I and A bands The A band, which is usually slightly longer than the I band in living muscle [illegible] contains the bulk of the [illegible]

about ten times as anisotropic as the I band. A number of other cross-bands and striae which have been recognized in the skeletal myofibril are indicated in Figure 2. Of these the Z line is a

prominent feature bisecting the I band and there is evidence that it runs continuously across the cell binding the myofibrils to each other and finally fusing with sarcolemma (Draper and Hodge, 1949). The only other banded feature which will be discussed here, and in which changes have been observed during contraction and stretch, is the H or Hensens disc. This is a

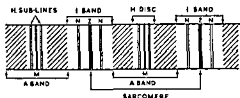


FIG. 2. Diagram showing cross-bands and lines of the skeletal myofibril.

rather broad band of lower protein density which appears in the centre of the A band when muscle is stretched (Hanson and H. E. Huxley, 1955) and which according to some authors is

the application of the electron microscope to the study of the ultra-structure of muscle has amply confirmed these views. These first electron microscope studies seemed to indicate that the myofibril was built up of parallel filaments running continuously through many sarcomeres. The filaments appeared to be 100–200 Å in diameter and to have a regular longitudinal periodicity of 250–400 Å. Cross-bands were considered to arise from the overlaying of other proteinacious materials, that occurring in the A band for instance was called the A substance.

It appears, however, that the fine structure of the myofibril is more complex than was originally thought, for the study of thin cross-sections with improved techniques has provided evi-

diameter which increase to 140 Å where they pass through the

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cent of the total protein consists of actin and myosin, and the remainder is made up of tropomyosin and possibly some other proteins not yet characterized. In the latter group would be included proteins of which cross-striae such as the Z line for example are composed, and those which might be presumed to be present to form a framework of stroma to support and bind the contractile proteins. Certainly an insoluble residue remains behind after myofibrils are extracted with solutions which would be expected to bring the recognized myofibrillar proteins into solution (Perry, 1953). Hanson and H. E. Huxley (1955) have some microscopic evidence that such material is present in the myofibril.

TABLE 1. Size and shape of the molecules of proteins obtained from the rabbit skeletal myofibril Data taken mainly from that collected by Bailey (1954)

Protein	Molecular weight	Thickness (Å)	Length (Å)
Myosin	420,000	25	2,300 – 1,500
Tropomyosin	53,000	~15	~400
Actin (monomer)	~70,000	~24	~290
Actin (dimer)	~140,000	~24 (?)	~580

It should be emphasized that the myofibril consists of a concentrated gel containing an average 15–20 per cent protein and will therefore constitute a comparatively rigid structure. The surrounding sarcoplasm may be even more concentrated with respect to protein (A. F. Huxley and Niedergerke, 1954) but as the proteins are in solution it will form a much less viscous system.

(a) *Myosin*. Myosin, which accounts for about 45 per cent of the total intracellular protein of skeletal muscle, is a globulin of high molecular weight (see Table 1). At pH 7 it is insoluble at ionic strength $(I) = 0\ 05$, but at higher ionic strength $(\sim 0\ 5)$ gives a viscous birefringent solution. Recent investigations (Laki and Carroll, 1955) suggest that the molecular weight is about 420,000, which value is lower than that previously reported (Weber and Portzehl, 1952). Furthermore physical investigations indicate that the molecule is very asymmetric—a property which is of importance in its structural and contractile roles.

H space. Lying between these A filaments and forming an interlocking hexagonal array with them are finer filaments of 40 Å. These fine filaments do not appear to be present in the H space but extend into the I band and are known as the I filaments. It

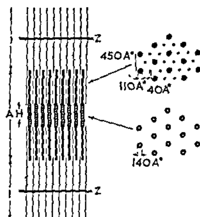


FIG. 3. Scheme for the fine structure of the skeletal myofibril. After Hanson and H. E. Huxley (1953, 1955).

has been postulated (Hanson and H. E. Huxley, 1955) that the actin filaments are joined across the H space by fine extensible filaments of protein, the S filaments. Such a scheme for the fine structure of the myofibril is illustrated in Figure 3.

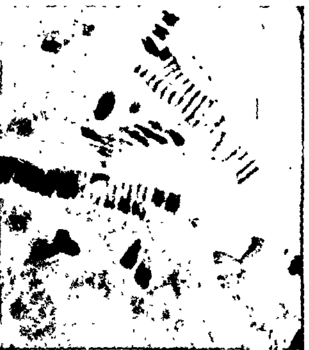
Methods for the preparation of myofibrils free from other formed elements and sarcoplasm (Schick and Hass, 1949; Perry, 1951, 1953; Perry and Grey, 1956) which will contract and simultaneously hydrolyse ATP have much facilitated study of the function and localization of the myofibrillar proteins. Before relating the latter to the structure of the myofibril it is necessary to say something of the properties of the proteins themselves.

PROTEINS OF THE MYOFIBRIL

Analyses of the isolated myofibril (Perry, 1952) indicate that it consists almost entirely of protein Very small amounts of fat, nucleic acids and inorganic material are also present but it is not possible to say at this stage whether the two former substances really form part of the structure or are merely adventitious contaminants arising during the preparation. Probably 80–85 per



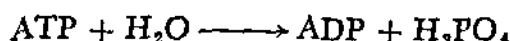
(*a*)



(*b*)

FIG. 4. (*a*) Myofibrils freshly isolated from rabbit skeletal muscle. Mag. × 2500. (*b*) Myofibrils after exhaustive extraction with 0·078 borate buffer pH 7·1 which extracts tropomyosin and actin in amount representing about 25 per cent of the total myofibrillar protein. Mag. × 2500.

A property of myosin which has greatly influenced our concepts of the biochemical basis of contraction is its adenosinetriphosphatase (ATPase) activity. The association of this enzyme with myosin was first demonstrated by Engelhardt and Ljubimowa (1939) and since that time many efforts have been made to separate the activity from the myosin, but the evidence available today indicates that the enzymic activity is a unique feature of the myosin molecule and not due to a contaminating protein. Purified myosin splits off the terminal phosphate from ATP, a process which is greatly activated by calcium.



$$ATP + H_2O \longrightarrow ADP + H_3PO_4$$

(*b*) *Tropomyosin.* Although tropomyosin is the most recently discovered myofibrillar protein it is perhaps the best characterized for it can be crystallized and lends itself to rigorous purification on account of its great stability compared to myosin or actin. Previous studies (Perry, 1953) on isolated myofibrils indicated that tropomyosin represents about 4 per cent of the total protein, but reinvestigation (Corsi and Perry, 1956) has indicated that there may be very much more of this substance present than was previously thought (probably about 12 per cent). As yet there is no indication of the function or localization of tropomyosin *in situ*, but it has been suggested (Kominz, Hough, Symonds and Laki, 1954) as an extension of some earlier ideas of Bailey (1948) that the myosin monomer is built up from units of actin and tropomyosin.

(*c*) *Actin.* The discovery of actin followed from the work of

the viscosity which rose again to the original value when the ATP had been hydrolysed. Similar observations were made by the Needhams and collaborators (J. Needham, Kleinzeller, Miall, Dainty, D. Needham and Lawrence, 1942) working independently. Subsequent work by Straub (1942, 1943) resulted in the isolation of actin which was considered to combine with myosin to form the complex actomyosin (myosin B). At

that time the fall in viscosity of actomyosin which ATP produced was explained as being due to the action of the nucleotide in dissociating the complex into actin and myosin; on complete breakdown of the ATP the complex would be reformed with the consequent return of the viscosity to the original high level.

Actin represents about 15 per cent of the intracellular muscle protein and as extracted by the method of Straub (1943) it is obtained in the so-called globular form (G-actin) which forms a solution of low viscosity. On addition of salt to solutions of G-actin it is converted to the fibrous form (F-actin) which combines with myosin to give actomyosin with the properties described above. This polymerization of actin, as it is described, possesses certain unusual features in that there are strong sug-

[illegible]

have thrown some light on the mechanism of the polymerization process.

(*d*) *Actomyosin.* Although the effect of ATP on actomyosin solutions was the first clear indication that ATP could produce a physical change in a protein system derived from the myofibril, this effect is not strictly analogous to contraction. If, however, actomyosin is precipitated in the form of a thread, on the *addition of ATP under the correct ionic conditions the thread* shortens down to $\frac{1}{4}$ or $\frac{1}{5}$ of its original length. The actomyosin thread shortens isodimensionally as the protein filaments of which it is composed are randomly oriented, whereas in the myofibril they all run parallel to the axis of shortening and consequently the myofibril contracts in the anisodimensional manner characteristic of living muscle. A model which is more comparable with the myofibril can be produced by orientating the proteins in these synthetic threads, but the protein concentration of actomyosin threads in general tends to be low and they are not capable of developing very high tensions on the addition of ATP. The glycerated fibre (Szent-Gyorgyi, 1949) is a much more satisfactory model, for on addition of ATP tensions are developed which are very comparable to those obtained

myosin in the light of the present views of the nature of the band changes occurring during contraction (see below). Recently Corsi and Perry (1956) have reinvestigated the protein fraction extracted from isolated myofibrils on treatment with 0·078 M borate buffer, pH 7·1 (Perry, 1953). After 10–20 days extraction of myofibrils prepared from fresh muscle ~25 per cent of the total protein passes into solution and the myofibril takes on the characteristic appearance shown in Plate XXV, Figure 4*b*.[1] The I band is extremely faint, the Z having disappeared altogether, whereas the H space becomes wider and much more distinct than it appeared in the freshly prepared myofibril (see Figure 4*a*). The soluble protein fraction obtained under these conditions consists mainly of tropomyosin and a form of inactive actin which is different in properties from both the F and G forms of this protein. Myosin does not pass into solution and the ATPase activity of the myofibril falls off very little during the extraction. *These investigations show that (1) there is very little* myosin in the I band, (2) myosin is probably not distributed evenly in the A band in myofibrils isolated from fresh muscle.

Changes in the Myofibril during Contraction

A complete description of the function of the myofibrillar proteins requires, in addition to a knowledge of their localization in the myofibril, an understanding of the band changes occurring during contraction. Due to the technical difficulties involved, descriptions given by histologists have been somewhat conflicting Recent studies on living single fibres with the interference microscope (A. F. Huxley and Niedergerke, 1954) and on isolated myofibrils from glycerated muscle made to contract by the application of ATP (Hanson and H. E. Huxley, 1955) are not subject to some of the errors which have complicated earlier studies. The latter two groups of workers have concluded that when muscle contracts to 65–70 per cent of the rest length (i.e. over the physiological range) the A band remains virtually unchanged in length, whereas the I band shortens. When more extensive shortening takes place the I band disappears and the edges of the A band make contact with the Z line to give the

[1] This plate will be found facing p. 320.

in living muscle. Glycerated fibres are made by fixing strips of fresh rabbit psoas at the resting length and storing them in 50 per cent (v/v) aqueous glycerol for several days at $-10°$. This procedure washes out the soluble proteins, much of the original ATP, and leaves a kind of contractile skeleton of the muscle cell. The myofibrils are oriented and held in position in the cell just as they are *in vivo*. Such preparations have been widely used as model systems for the study of contraction and relaxation.

Localization of Proteins in the Myofibril

On the basis of studies of the birefringence of isolated myosin and whole muscle Weber (1934) suggested that there was a concentration of this protein in the A band. It had been noted by several workers that the intensity of the A band fell during the extraction of myosin but direct demonstration that most of the myosin was concentrated in the A band was provided by the independent investigations of Hasselbach (1953) and Hanson and Huxley (1953). Hasselbach showed that when myosin free from actin was extracted from fresh muscle the A band was no longer apparent on electron microscope study of the myofibrillar residues. Hanson and Huxley observed somewhat similar effects when myofibrils isolated from glycerated muscle were perfused with solutions which selectively extracted myosin. The latter workers did point out, however, that the centre of the A band, the H disc, was not so readily extracted under these conditions.

After extraction of the myosin long continuous filaments could be seen and the postulate that these consisted of actin was [illegible] the A filaments in their model consisted of myosin, whereas actin was localized in the I filaments.

The possibility that the myosin is localized in the A band is not apparently acceptable to all workers (see A. G. Szent-Gyorgyi, Mazia and A. Szent-Gyorgyi, 1955); certainly it does present some difficulties in explaining the contractile role of

Hill, 1955) to suggest that the binding of ATP to the contractile protein system is sufficient to produce contraction and that contraction itself is independent of dephosphorylation of ATP. Morales *et al.* (1955) consider that the contractile element (actomyosin) is kept fully extended due to the mutual repulsion of positive changes distributed along the length of the element (Figure 5). On addition of ATP, which exists in solution under physiological conditions mainly as a negatively charged ion (ATP^{4-}), the nucleotide is bound and neutralizes the positive charge on the contractile element so that the extending electrostatic force disappears. Consequently the actomyosin element will shorten under the influence of thermal agitation forces (see Figure 5).

From time to time it has been suggested that the splitting of ATP by the actomyosin system involves phosphorylation of the protein. The various mechanisms for contraction of phosphorylated myosin which have been suggested range from that proposed by Riseman and Kirkwood (1948), who postulated that phosphorylation of hydroxyamic acids would modify the extending electrostatic force so that 'entropic contraction' of the type adopted by Morales *et al.* (1955) would take place, to those favouring a mechanism involving formation of covalent links between different points on the polypeptide chain of myosin in such a way that the chain must fold (Binkley, 1945; Weber, 1955). Such a mechanism is illustrated in Figure 6

Using ^{32}P labelled ADP Koshland, Budenstein and Kowalsky (1954) were unable to demonstrate the formation of a phosphorylated myosin intermediate during the hydrolysis of ATP They concluded that if such an intermediate existed it was of transitory nature, but Morales *et al.* (1955) consider that Koshland's results are consistent with a binding-contraction rather than a phosphorolytic cleaving-contraction mechanism. The latter conclusion is, however, not unequivocal as Weber (1955) has recently reported evidence for the existence of a phosphorylated myosin intermediate during the interaction of myosin and ATP.

Although it is apparent from the above discussion that an adequate description cannot yet be given of the relation of the

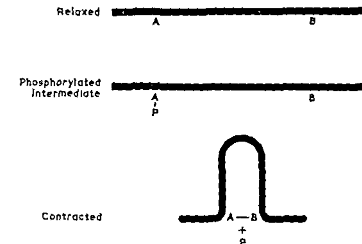
appearance of reversal of striation which is characteristic of strongly contracted muscle. On stretching the myofibril over the range within which length changes are reversible, the length of the A band is likewise unchanged for extension appears to be confined to the I band only.

Enzymic Activity of the Myofibril

Of the three well-characterized myofibrillar proteins only myosin has so far been demonstrated to possess any enzymic activity, namely ATPase. Consequently the intact myofibril has marked ability to liberate inorganic phosphate from ATP, but it should be stressed that there exist considerable differences in properties, particularly with respect to the activating effect of ions, between the myofibrillar ATPase and myosin when they are studied under conditions comparable to those existing in the cell. For instance whereas only calcium will activate myosin ATPase the myofibrillar enzyme is activated both by calcium and magnesium. The isolated myofibril freed from sarcoplasm usually possesses 5-adenylic deaminase and myokinase activity (see Perry, 1956) but these enzymes do not appear to play any part in contraction and are probably contaminants not readily removed by the repeated washing procedures used during the preparation of myofibrils.

Assuming that the energy made available on the hydrolysis of ATP provides the energy for contraction one might expect that contraction and dephosphorylation would be closely linked processes. Many workers (Weber and Portzehl, 1952, 1954; Bendall, 1953a; Bozler and Prince, 1953) have provided evidence that there is a close correlation between the level of ATPase activity and the rate of shortening in model systems of actomyosin threads or glycerated fibres. Somewhat different evidence supporting the same view has been obtained by Perry (1954) from the coupled creatine phosphokinase and myofibrillar ATPase systems. Nevertheless several reports are to be found in the literature which throw doubt on the view that dephosphorylation is a necessary requirement of contraction. Such examples and certain physico-chemical considerations have led Morales and his collaborators (see Morales, Botts, Blum and

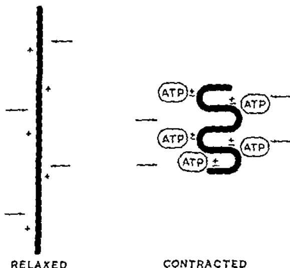
band which apparently do not change in length. Some evidence of density changes within the A band during ATP-induced contraction of myofibrils isolated from glycerated muscle has been reported (Hanson and Huxley, 1955) and possibly these may reflect changes within the A filaments.



[illegible]

Biochemical analyses of the changes occurring during the phases of a single twitch in living muscle offer an approach to the problem of studying the chemical events which accompany contraction *in situ*. The technical difficulties are considerable but with the aid of chromatographic methods some progress has been made. The recent results of Fleckenstein, Janke, Davies and Krebs (1954) indicate that inorganic phosphate is produced during a single twitch but it is not clear from which compound this is derived. These workers and, independently, Mommaerts (1954) confirm Fleckenstein's (Fleckenstein, Janke and Elke, 1954; Fleckenstein, Janke, Lechner and Bauer, 1954; Fleckenstein and Janke, 1953) earlier findings that the level of ATP and ADP is unchanged during a single twitch. Whilst it is generally

enzymic to the contractile changes, it seems indisputable that the interaction of ATP with the actomyosin system can cause contraction to take place. Until recently contraction had been demonstrated in model systems containing actomyosin and not with either protein alone, yet myosin has usually been considered



[illegible] Scheme in which the binding of ATP induces contraction. The [illegible] agitation forces.

to be the contractile partner. This view is supported by recent experiments of Russian workers (Ashmarin, 1953; Kafiani and Engelhardt, 1953) who have reported that ATP can bring about the contraction of threads made from surface films of actin-free myosin. This effect was obtained at pH 9 but could be obtained at physiological pH values in the presence of certain dyes and suggests that the role of actin may be to modify the charge distribution on the myosin.

It is difficult to reconcile a contractile role for myosin with the changes in striation occurring on contraction if the model proposed by Hanson and Huxley is accepted. This would mean that moderate contraction involves a shortening of the I (actin) filaments mediated in some way by the myosin filaments in the A

activity associated with the shortening of glycerated fibres, during relaxation the ATPase activity is low. It follows therefore that ATP has a dual function when interacting with the actomyosin system, namely:

(1) contracting action associated with a high rate of ATPase activity,

(2) relaxing or plasticizing action associated with the low rate of ATPase activity which occurs in the presence of relaxing factor.

As yet there are no clear ideas on the nature and action of the relaxing factor although relaxing activity has been claimed for a number of enzymes, e.g. myokinase (Bendall, 1954), creatine phosphokinase (Goodall and Szent-Gyorgyi, 1953; Lorand, 1953) as well as for
pyrophosphate (W
and ethylenediami
1955).

A study of the properties of the hydrolysis of ATP by isolated myofibrils (Perry and Grey, 1956) has shown that the inhibition obtained by higher ATP concentrations is markedly dependent on the magnesium concentration when this cation is the activator (see Figure 7). This effect is a feature of magnesium activation and is not obtained when calcium is the activator. Hence at a given ATP concentration when adequate magnesium is present the rate of ATP hydrolysis is high but if the magnesium is removed from the system by various complexing agents the ATPase activity falls to a low level due to a relative excess of ATP. This condition of substrate inhibition is considered to be characteristic of relaxation in glycerated models and it is suggested that the role of the relaxing factors is either to bind magnesium or to maintain the ATP at a high concentration so that the ATP is in relative excess and its relaxing action becomes dominant. Certain properties of the substrate-inhibited magnesium-activated ATPase support this view; for example the effective relief of substrate inhibition by low concentrations of calcium is paralleled by the effect of similar concentrations of calcium in inhibiting relaxing factor action (Bozler, 1952; Bendall, 1953a).

agreed that the ATP level may fall on more prolonged activity, other workers (Mommaerts and Rupp, 1951; Munch-Petersen, 1953) have claimed that a fall in ATP and increase in ADP can also be demonstrated after a single twitch. If the results of Fleckenstein *et al.* and Mommaerts are valid they raise the question whether some substance other than ATP is the source of the inorganic phosphate produced in contraction. There is no evidence as to what this substance might be, if indeed it exists at all; the other nucleoside triphosphates (inosinetriphosphate, uridinetriphosphate and guanosinetriphosphate) which actomyosin readily hydrolyses have come under suspicion but some results of Hasselbach (reported by Weber, 1955) on their ability to induce the relaxation of glycerated fibres appear to exclude these substances. Certainly *in vitro* ATP will induce contraction of the isolated myofibril which is completely free from the other nucleoside polyphosphates.

Relaxation

Although this lecture is intended to deal with the muscle proteins and contraction it would not be out of place to conclude with a few remarks about their role in relaxation. If the isolated myofibril is treated with ATP of the same concentration as that found in the cell and in a similar ionic environment, it hydrolyses the nucleotide rapidly and contracts. In resting muscle the rate of inorganic phosphate production is very low, suggesting that there is present in living muscle some factor which inhibits the myofibrillar ATPase activity and thus prevents contraction.

The work of Marsh (1952), Bendall (1953a), and Bozler (1951) has shown that indeed this is the case. This substance, which is known as the relaxing factor (there may be two components, see Kumagai, Ebashi and Takeda, 1955), is considered to be effective in resting muscle but somehow its inhibitory effects are lifted during contraction so that the ATPase activity rises and the myofibril contracts.

In the presence of partly purified preparations of the relaxing factor, glycerated fibres which had previously been contracted by the addition of ATP will relax if ATP and magnesium are present. Furthermore in contrast to the high level of enzymic

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Conclusion

Although considerable advances have been made in describing the structure of the contractile units in terms of their protein components, much remains to be done. A great deal of biochemical knowledge is available and it is fair to say that the

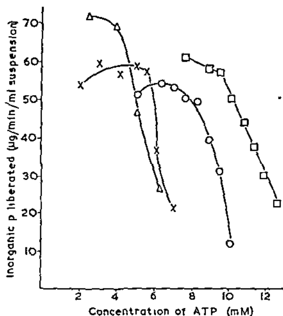


Fig. 7. Effect of $MgCl_2$ concentration on the inhibition of the myofibrillar ATPase activity by excess substrate Incubations were carried out in 0 05 M trishydroxymethyl-amino-methane buffer, pH 7·4, for 5 min at 20·5° C.

△ 2 5 mM-$MgCl_2$
× 5 mM-$MgCl_2$
○ 7·5 mM-$MgCl_2$
□ 10 mM-$MgCl_2$

muscle cell provides one of the outstanding examples of progress towards the aim of integration of biochemical function with morphological structure. Nevertheless the nature of the fundamental relationship between chemical events and mechanical changes has yet to be determined. What is clear is that the normal structional changes in the myofibril are determined by enzymic changes related to both myofibril and sarcoplasm.

XIX

Observations on the Excitable Cortex in Man

J. A. V. BATES

At the end of the last century there was a unique convergence of thought and discovery in the fields of comparative anatomy, physiology, pathology, histology and clinical neurology, and there emerged a new set of beliefs concerning the organization of the efferent side of the central nervous system. It was postulated that motor centres existed in the cerebral cortex; centres wherein the faculty of voluntary movement resided; centres evolutionarily more recent than spinal motor centres; centres wherein were represented movements in the most differentiated degree; centres from which voluntary nervous impulses were discharged via the pyramidal pathway. This scheme, which I shall refer to as the classical hypothesis, was proposed notably by Ferrier, Gowers and Schaefer, and with important reservations by Hughlings Jackson. It was opposed by some clinicians, notably Bastian, and most Continental neurophysiologists. There is a great deal to be learnt from study of the various controversies that followed, but the person whose views most concern us today studiously kept apart from the polemics and was content to contribute a few vital facts of observation from an experience which no one before or since has rivalled in its scope—his name of course was Sherrington.

During the past five years at the National Hospital for Nervous Diseases, Queen Square, London, thanks to the help given by Dr. Carmichael, Mr. McKissock and their various assistants,

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Sherrington, however, commented on it indirectly from his experience of stimulating over forty chimpanzees (Leyton and Sherrington, 1917). He noticed that particular movements that he could readily obtain in one animal could not be obtained in another animal and vice versa, and he discussed the extent to which these differences could reasonably be attributed to accidents of technique or anaesthesia, and more especially to the differences in configuration of the cortical gyri in different animals—for about one-third of the excitable cortex in any animal is normally buried in sulci. He concluded that these various factors were insufficient to account for the differences between different animals and it seemed therefore to him that an 'individuation' of response must be postulated. I have made observations on four cases where we have re-explored the motor region on a second occasion some months later (Bates, 1953b). It has been found that the repeatability of the excitable points in a topographical sense is very high and that particular individual characteristics in the response seen on the first occasion are repeated on the second. In other words it seems in man also that both the anatomical fixity and the details of movement differ in a consistent way between individuals.

Now the conventional idealized diagram of the cortex with the words Face, Arm, Leg inscribed on the precentral gyrus has been developed by Penfield's artist into the well-known homunculus. Penfield in this room three years ago (Penfield, 1954) reminded us that 'this is no more than a mnemonic to recall the peripheral connexion of each part of the gyrus'. But I think three other points about the homunculus should be stressed. First, that as a summary it discards a large amount of data, for the movements which were actually observed are nowhere recorded. Second, that we are in the hands of the artist rather than the statistician for this concept of the average, for the amount of topographical variation between individuals as shown by Penfield's own protocols is very considerable. Third, that there is a danger that this average is thought of as having a real existence in each of us so that departures from it in an individual protocol are put down to insufficiently thorough exploration or other incidents of technique Sherrington would not

I have had an opportunity to make observations on the excitable motor cortex exposed at operation on man, and I shall discuss certain observations which are relevant to the foundations of the classical hypothesis of cortical motor centres. Although these observations on man are rather fragmentary, I think they are significant because they seem to be complementary to some observations which Sherrington made under very different conditions on monkeys and apes.

The technique has been given in more detail elsewhere (Bates, 1953a), but in brief we have stimulated the cortex electrically in sixty cases of various types of cerebral disease, forty of which have had a hemispherectomy. There have also been occasions when we have felt justified in stimulating the cortex when there was no obvious adjacent pathology. The patients have all been very lightly anaesthetized with nitrous oxide, oxygen and Pethedine. A 2 mm. bipolar stimulator has been used delivering interrupted DC from a low-impedance source in the form of 50 square pulses per second of 4 msec. duration each. The cortex is stimulated for 3 sec. at each application and the excitable points are marked by numbered tickets. Cine films are taken of all the motor responses, and study of these forms the basis of my material.[1]

Repeatability of Responses

Now before we face the problem of describing the responses that follow the stimulus and interpreting them, there is a question which naturally arises at the very outset—are the responses to stimulation repeatable? It has long been known that if you repeatedly stimulate the same cortical point under certain optimum conditions, the motor response remains unchanged. But the more significant question is—what is the long-term repeatability? That is to say, how do the motor map and the responses at one exploration compare with those at a second exploration some months later? There is surprisingly little in the literature on this in view of its importance, in fact I have not a single series of animal experiments specifically designed to answer it.

[1] This lecture was illustrated with cine films, but single frames from films make unsatisfactory illustrations and none have been included here

PLATE XXVI


(a)


(b)


(c)


(d)


(e)


(f)

accept this assumption for the chimpanzee and it would not appear to hold for man.

On the evidence from man it seems that the map of the excitable points and the details of the responses are as individual as the face or fingerprint and hence it is not unreasonable to suggest that we may be dealing with a system with a pronounced genetically determined element. The particular movements obtained in an individual would seem then to be a selection out of a larger class available to the species, similar in fact to his particular blood groups. This of course is speculative, but it seems at least that the responses to a single stimulus have a sufficient degree of long-term repeatability to make it worth discussing the difficult question of how to describe and interpret the movements observed.

Cortical Stimulation and Reflex Movements

Ferrier (1886) considered that he had evoked by stimulation the distinctively voluntary or purposeful movements of his various animals and he even went so far as to suggest that stimulation would evoke any special tricks of movement learnt by the particular animal during its life. Clearly his belief in highest motor centres would have been justified if this belief could have been verified. Schaefer (1900) supported Ferrier's scheme and published a myogram to illustrate the similarity between voluntary movement and cortically induced movement in the monkey.

Sherrington, I think, was among those who never completely identified themselves with this interpretation. He stressed particularly the fractional nature of the movements and would not commit himself to the word 'purposeful' to describe them. We must surely agree that the word 'purposeful' introduces yet another confusing element, for any movements which successfully achieve a recognizable end can be called purposeful and these would include the escape movements of the spinal frog or the feeding movements of protozoa. Clearly any word that is based on a subjective opinion of what may be behind the movement must be discarded in describing it. The only approach open to us is to record as accurately as possible what is observed

and afterwards to see if any similar movements or postures are observed under any other condition. This was Sherrington's method, and he was struck by the resemblance between the movements he evoked in his animals by cortical stimulation and the movements he evoked by sensory stimulation in the same species of animal under a spinal preparation. In 1892 he wrote 'Flexion and adduction of the hallux with extension of the other digits . . . I have frequently seen occur as a spinal reflex movement in the foot of M. Rhesus, just as one frequently sees it occur on excitation of the leg area of the hemispheral cortex.' And he wrote in 1898, 'Flexion adduction of the thumb [in a monkey] though instanced as an action of peculiarly cortical nature, is really the most frequent and facile pure spinal reflex of the upper extremity', and in more general terms in *The Integrative Action* (1906): 'The local reflex movements obtainable from the bulbo-spinal animal and the reactions elicitable from the motor cortex of the narcotized animal fall into line as similar series. Both consist of the same group.' We cannot make observation on bulbo-spinal human preparations as he could on the dog and monkey, consequently we cannot discuss with the same confidence the nature of motor organization at a spinal level in man. But the problem which Sherrington poses is whether or not we can show a resemblance in man between the response to cortical stimulation and certain types of movement which on other grounds we may feel justified in believing are organized at a spinal level.

Clinical neurology recognizes two main classes of reflex movement, the deep and the superficial. The deep reflexes are a muscle twitch caused only by a sudden stretch and localized to the muscle or muscle group stimulated by stretching. They are relatively similar from person to person They are normally equal on the two sides of the body, and the movements observed are explained by the facts of muscle and bone anatomy. The superficial reflexes are, in contrast, ill-defined and unexplained. This group of phenomena includes movements variously called postural reflexes, associated movements, reflexes of spinal automatism, defence reflexes, flexor withdrawal reflexes. By far the most notorious superficial reflex is the

discrete finger movement, when evoked by cortical stimulation, is evidence of the evocation of a skilled movement. Films have been taken of normal infants during the first 48 hours of life when they are awake and relaxed (i.e. during the few minutes in the 24 hours when they are neither sleeping, feeding nor crying), and it is at once apparent that the infant has been born with an abundant supply of discrete finger movement. In fact movements of any particular finger can appear more independent [illegible]

evoked by stimulation, one cannot necessarily assume that one has evoked movements that would not have existed save for consciously directed practice. What the growing child acquires is a measure of control over the mechanism for discrete movements he is supplied with, and it is necessary to keep clear the distinction between a mechanism for discrete movement and an ability to control the discrete movement. It would be helpful to know whether or not infants born with grossly deficient cerebral development show discrete finger movement, since they may be the nearest we ever get to a bulbo-spinal preparation. I have not yet had the opportunity of filming movements in such a case, but from what others have told me it seems likely that these infants at birth do show the same differentiation of finger movement as a normal infant.

This digression has been necessary to establish that discrete finger movement when evoked by cortical stimulation is not necessarily evidence of differentiation through practice, and we can now continue with the main question provoked by Sherrington's observation on the bulbo-spinal monkey. These observations arouse a suspicion that in cortical stimulation one is merely activating particular movements or changes in posture that are provided for by nervous arrangements outside the cortex, presumably at a spinal level. Observations on man give evidence for this of three different kinds

In the first place, if these movements are to be looked upon as organized at a spinal level it would be helpful if cortical stimulation actually would evoke the best recognized superficial

Babinski phenomenon, but many others alleged to be of value in clinical neurology have been described. They are distinguished from deep reflexes in several important ways. As a group they are elicited by a variety of stimuli which include scratching the skin, stretching the skin, slow stretching of muscles. Stimulation is effective over relatively wide zones; the responses have a relatively long latency; the movements are more generalized and sometimes bilateral; the superficial reflexes are more susceptible to fatigue and to the influence of the subject's attention; and lastly, they show greater variation in the normal and in particular may not be the same on the two sides of the body. Thus a problem arising out of Sherrington's observations is whether or not the movements in response to cortical stimulation in man resemble movements in the general class of superficial reflexes.

Let me begin with a negative statement. Penfield (1954) has stressed that nothing resembling a skilled movement is ever seen in response to cortical stimulation. This raises a question as to what is a skilled movement, but it does seem that nothing resembling a movement which one recognizes as having been acquired by practice and repetition is ever seen in response to cortical stimulation. For example, consider a simple movement which is seen from about six weeks onwards in the infant in which the back of the hand, the base of the thumb, and after hours of practice the tip of the thumb is brought neatly to the mouth. This requires a particular co-ordinated behaviour of muscle groups acting on the shoulder and elbow, and although it is not uncommon to see stimulation produce movement at both the shoulder and elbow, I have never seen the hand or any part of it brought to the mouth in response to stimulation. If this hand-to-mouth movement, a movement that is practised daily by all of us, is not seen, one might not expect to see other less frequently practised movements. But skilled is also taken as synonymous with delicate or discrete, and on this basis it might be asked—are not discrete movements of the thumb and individual fingers in fact movements acquired by practice—are they not movements differentiated out of grosser movements by consciously directed effort in the young child? If this is correct, then

middle fingers and this posture has been said to show inherited familial tendencies—from my own observation, about 1 in 10 of the males I can frequently observe adopt this posture involuntarily some time during the day. It is also seen in some chronic hemiplegic hands, and is illustrated in Gowers's *Textbook of Neurology* from a case of athetosis. I have seen this posture produced in two cases from cortical stimulation.

Figure 1*c* illustrates an associated extension of the outer three fingers with the thumb and index opposed. The little finger is most extended and this posture is seen in some people holding a tea-cup. It is commonly thought to be an affectation, but it is seen in the infant, especially at the nine months stage, when thumb-index opposition begins and I think should be regarded basically as an 'associated movement' occurring in association with the pincer-action of the thumb and index. One of the commoner cortical response synergies involves extension of the outer three fingers. The extension often commences in and develops to a fuller extent in the little finger and it leads to the posture illustrated.

Figure 1*d* is of the familiar pointing gesture of the notice-board—the fully extended thumb and index and fully flexed third, fourth and fifth. This posture is the opposite of *c* and is one seen in the outstretched hand in a postural role and in the infant before the nine to twelve months' thumb-index period, as well as during it. This line of inquiry started from the coincidence of seeing on the same day this particular hand posture produced by cortical stimulation and the same posture assumed in the fully extended left arm of a footballer photographed at the instant of a strenuous right-footed kick.

Figure 1*e* is one of the old hand signs used in religious blessing, known as the *mano pantea*. Occasionally cortical stimulation of the hand area gives no evidence of the thumb-index differentiation, but instead the index and middle fingers move as a unit and produce this posture in extension.

Figure 1*f* with the interphalangeal joints of the fingers extended is the *main figee* or congealed, or the *main d'accoucher*. When combined with some flexion and adduction of the metacarpo-phalangeal joints and the wrist, it is the hand of tetany.

reflex movement, namely the Babinski plantar response, in suitable cases. I have previously reported (Bates, 1953a) on the results of stimulation of the medial surface of the sound hemisphere in ten cases, and in two of them a response has been observed which closely resembles the crossed Babinski phenomenon. That is to say, an up-going toe in the hemiplegic foot (which is ipsilateral to the cortex stimulated) together with spreading of the other toes, some flexion of the hip and a flexor toe response on the sound (contralateral)side. I have also seen isolated dorsiflexion of the contralateral great toe from stimulation of the internal capsular fibres after hemispherectomy.

The second set of evidence to which I would call attention concerns the hand. It seems there is a resemblance between certain of the postures which the normal adult's hand is seen to adopt in the unattended-to state and certain of the postures of the wrist and fingers that follow stimulation of the normal cortex. Hand postures are easy enough to observe in daily life though very difficult to record. Data is to be found in press photographs of the 'candid camera' type, and to some extent in the literature of gesture and hand-sign languages. Plate XXVI, Figure 1[1] illustrates some of the postures in question.

Figure *1a* shows the left hand in the position of rest. Note that the index is characteristically less flexed than the outer three fingers and note also the upper transverse flexure line which turns upward to end on the web between the index and middle fingers. This is also shown in *e*. The ending of this flexure line is one of the cardinal distinguishing features of the human hand; in all monkeys and apes it crosses the palm to the radial border. It is concomitant with the 'aloofness' of the index finger from the behaviour of the remaining fingers which Wood Jones (1941) commented on. It is relevant to note that this flexure line is present from about the tenth week of foetal life onwards, well before individuation of index-finger movement by practice could be effective.

Figure *1b* shows a posture which has been described since the days of Ovid as the *manus obscaena*, for obvious reasons. More usually, perhaps, the thumb comes between the index and

[1] This plate will be found facing p 336

after-movements are far less likely to occur. But it is not difficult to obtain the smallest discrete movements from stimulation of the fibres as they pass through the internal capsule.

Thus from the mere character of the movement or change in posture in an individual case there is little to convince one on the evidence of stimulation that the grey matter is playing a significant role.

Let me at this point recapitulate the argument so far. The movements evoked by cortical stimulation were originally likened to voluntary or purposeful movements. But these labels owe their origin to a pre-existing hypothesis of cortical motor function. If the hypothesis is questioned, the likeness seems questionable. One can readily say what the movements are not like, but so far as I can see only Sherrington has called attention to what they seem to resemble. He said they resembled in detailed character and ease of production some of the movements that you would obtain reflexly by sensory stimulation in the spinal preparation of the same species: he also suspected that they have an individuality, at least in apes. It seems one can get complementary evidence in man which is consistent with his views, although the support is, naturally enough, indirect.

Sherrington, it will be remembered, observed isolated thumb movement as a pure and facile spinal movement, and I have emphasized that newborn infants have a large repertoire of discrete finger movement. This does not prove that such movements are organized at a spinal level, but it suggests they may be, and it does establish that they are differentiated from gross movements without deliberate practice. Secondly, at least one complex response-movement widely regarded as a spinal automatism—the crossed Babinski response—can be produced by cortical stimulation in an appropriate human preparation. Thirdly, stimulation may provoke certain postures of the wrist and fingers which are characteristic of those adopted involuntarily in normal people and which are variously classified as postural reflex movements, associated movements, reflexes of spinal automatism Lastly, a variety of responses, including discrete finger movement and characteristic hand postures, can be

But it is also a not unfamiliar posture in the hand of orators, and since it is also described by patients illustrating the form of their focal epilepsy it is not surprising to see that it is also produced by stimulating the cortex.

There is some evidence therefore that so far as the hand is concerned, there may be a similarity between the details of its associated movement and involuntary posturing, and the responses to cortical stimulation of the hand area. Although we do not know enough of what lies behind these postures to say that they represent the activity of intact neurone organizations at a spinal level, this similarity is relevant to any interpretation of the cortical motor response.

The third piece of evidence relevant to Sherrington's observations is of a rather different nature.

If we consider how we could test the hypothesis that stimulation gives evidence of cortical motor centres, it would be instructive to compare the responses between stimulating the outer layer of the cortex and the fibres leaving it, say, in the internal capsule. This is tantamount to asking 'Because stimulation of the cortex produces movement, can you infer that you have demonstrated centres for movement peculiar to the grey matter?' This was the inference of Ferrier and others. But a few months after Ferrier's paper appeared (in 1873), Burdon Sanderson (1874) showed that all the movements that could be produced by stimulation of the grey matter in the cat could be produced equally readily by stimulation of the white fibres after the grey matter had been cut away. Sherrington (1906) went even further and showed that inhibition of movement could be produced by capsular stimulation.

In observations on man Penfield has confirmed Burdon Sanderson's old results and so have I (Bates, 1953c). So far as the detailed character of the movement or of the resulting posture is concerned, stimulation of the white fibres and the grey matter gives similar results in a given individual, save that when stimulating the capsule the motor disturbance may be more extensive due to intermingling of descending fibres. There are, however, differences. Without the grey matter the latency between stimulus and response is invariably short and clonic

a partial hemiplegia of many years' duration. But there are cases (four out of thirty-nine) where such wrist and finger movements as these have remained unchanged in spite of removal of the hemisphere, which has been demonstrated to contain excitable motor points. It appears from histological examination that the cortex beneath these points has been undisturbed by the disease process. I would emphasize that it is not that function returns to these patients by a process of recovery, but that what function they have is never in the least disturbed further by the operation —it is present unchanged on coming round from the anaesthetic. And film records confirm the detailed similarity between particular movements they can make to order, and movements evoked by stimulation of their cortex which is by now in the pathologist's bottle.

These observations, I think, suggest that one of the pillars of [illegible]

so. And it is relevant to point out that stimulation and ablation are by no means complementary techniques, taking the normal cortex as a whole. Those familiar with Penfield's accounts of his operation will not need me to expand this. Excision of a region producing phonation is not followed by permanent speech difficulty; of a region producing somatic sensation is not followed by anaesthesia; of a region producing complex auditory and visual recall phenomena is not followed by failure to recall subsequently the particular phenomena. And more especially relevant, there is a region on the medial surface from which complex movements are evoked, which Penfield has called the Supplementary Motor Area. Excision of this excitable motor region is not followed by motor deficit. None of all this was known to Ferrier and his contemporaries, but we cannot ignore it and I believe there are sufficient grounds for suspecting that the pre-Rolandic area may be a special case in the sense that the superficial concurrence between stimulation and ablation in that region may be, so to speak, a major physiological red-herring. Penfield (1954) has made the suggestion that when motor function partly recovers, there is a recovery of precisely

obtained by stimulation of capsular fibres similar to those obtained from the cortex.

I submit that these observations, taken together with Sherrington's, naturally lead to the question whether, on the evidence of stimulation alone, there is anything to suggest a higher order of motor representation in the cortex. Would not a sufficient hypothesis *on the evidence of stimulation* be this—that there are a set of motor organizations at a spinal level and various nervous pathways are afferent to them, one set coming from the skin and deeper structures via the dorsal roots, others from the brain? We might look on the cortico-spinal tract as essentially an afferent tract to these centres as did François Frank in 1887, and we might line ourselves with other contemporary critics of the hypothesis of Ferrier and Jackson and hold that there is no more significance in the statement that movements are represented in the cortex than there is in the statement that movements are represented in the skin.

But perhaps it might be said this is surely going too far—the evidence of stimulation was only one of the pillars on which the classical hypothesis rested. Surely in the first place the consequences of ablation of the precentral gyrus entitle one to think of cortical motor centres

Evidence of Ablation

Let us then consider separately the evidence of ablation of the excitable motor region. It could be held until recently that the results of ablation were complementary to those of stimulation, in the sense that there *invariably* followed a loss of the particular movements that stimulation had evoked. We now know that the word 'invariably' is not true in a special case.

Krynauw (1950), Welch and Penfield (1950), besides ourselves (Bates and McKissock, 1951) have all reported that in cases of infantile hemiplegia there may be no further impairment of motor function following removal of a diseased hemisphere, which may contain quite a number of motor points giving movement of the opposite diseased limb when stimulated.

I would emphasize first that in our material this observation is exceptional—the paresis of the upper limb is usually increased by the operation and complete paralysis may follow, in spite of

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those very movements that stimulation evoked. In so far as the classical hypothesis of the motor system was based on a belief in the complementary nature of the evidence from stimulation and ablation, this is about as direct a refutation of it as one could have. At present it is perhaps somewhat beyond the recorded facts of observation, but it is a very important suggestion to explore.

Summary and Conclusions

For the past eighty years an hypothesis has been widely accepted as a basis for discussion of the motor system. It is held that there are motor centres in the cerebral cortex wherein the most finely differentiated movements are represented and that the activity of these centres is responsible for voluntary movement. One of the grounds for this belief is the observation that stimulation of a part of the cortex may produce fine discrete movements. But this is not conclusive evidence for the presumed centres for as Sherrington observed, movements of the same class can be produced by sensory stimulation in the bulbo-spinal animal, and observations on man indirectly strengthen Sherrington's criticism. In the first place, a mechanism which can produce discrete finger movement is developed and in working order in the infant at birth. Secondly, cortical stimulation in man characteristically produces movements or changes in posture which resemble those in the general class of superficial reflex movements, movements of spinal automatism or involuntary movements. Thirdly, fine finger movements identical in character with those produced by cortical stimulation have been produced by stimulation of the internal capsular fibres.

A second ground for the classical hypothesis of cortical motor centres is the observation of paralysis which follows ablation of the cortical motor region—and the deduction that cortical stimulation and ablation are therefore complementary techniques in the sense that they are in a peripheral nerve. But it is now clear that in other cortical regions their evidence is not complementary, and in cases of long-standing hemiplegia ablation of an excitable motor region may be followed by no further paralysis In the light of these considerations it would appear that the classical hypothesis is in need of revision.

seems to indicate that some form of volume receptor is concerned in the control of emptying. Not only was the intersubject variation small under these conditions but the majority of subjects showed consistent responses from day to day. As may

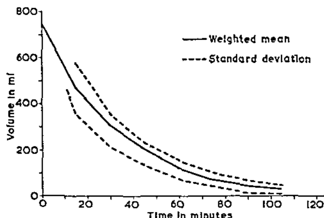


FIG 1. Volume of meal remaining in stomach plotted against time (Hunt and Spurrell, 1951).

be seen in Figure 2 the normal emptying pattern is also found in patients with duodenal ulcers. The ordinate shows the volume of the test-meal in the stomach plotted on a logarithmic scale, and the abscissa shows time. Each point, which represents the result of a separate test-meal on a separate day, falls close to the straight line. Hundreds of similar experiments have shown that the stomach usually behaves consistently from day to day under standard conditions. This exponential type of emptying pattern was first described by Marbaix in 1898 and has since been ... nd Spur ... 53) and l ... to note that the relation between the intragastric volume and the gastric output was observed before the somewhat similar relationship described for the heart in Starling's Law (1918). The relative outputs of the heart and stomach as pumps may be judged from the fact that the maximal volume entering the

XX

The Investigation of Gastric Digestive Function in Man

J. N. HUNT

THE purpose of this lecture is to draw attention to some methods of investigating gastric function and to show how the results of such studies may be interpreted with particular reference to patients with duodenal ulcer.

STUDIES OF GASTRIC EMPTYING

The reliability of measurements of gastric emptying

Under standard conditions the stomachs of different people empty at different rates but the smallness of the variation between subjects under some experimental conditions is remarkable. Figure 1 shows the mean emptying pattern in nineteen students for a standard test-meal of 750 ml. of a solution of pectin and phenol red containing 35 g. sucrose/l. The ordinate shows the volume of the meal remaining in the stomach, the abscissa shows time. These data were obtained by giving 190 standard test-meals on different days and recovering the gastric contents after varying intervals of time. As two-thirds of all the results fell within the area enclosed by the broken lines, it is clear that there was little intersubject variation in gastric emptying in these experiments. The volume leaving the stomach per minute becomes progressively smaller during the digestive period in such a way that a constant percentage of the volume of the meal in the stomach leaves every minute during the main part of the digestive period. An emptying pattern of this kind

inhibit emptying. Table 1 lists some of the components of the regulating machinery which must be borne in mind when devising a test to assess maximal gastric emptying power.

TABLE 1. A scheme for the regulating mechanism of gastric emptying

Stimulus	Receptors	Effect
Acid in meal	Precardial	Slows emptying
Increase in volume of meal	Gastric	Hastens emptying
Acid in meal	Postpyloric	Slows emptying
Glucose, potassium salts and fat, in meal	Postpyloric	Slows emptying
Volume of gastric outflow	Postpyloric	Slows emptying

To find the most suitable volume of meal to use in assessing maximal gastric emptying power studies were made of the relation between the original volumes of a standard test-meal containing 35 g. sucrose/l. and emptying patterns (Hunt and Macdonald, 1954). A typical result for one subject is shown in Figure 3. The ordinate shows the rate of emptying in ml. per minute; the abscissa shows time. Paying attention first to the period 0–10 minutes it may be seen that the larger the meal the greater the initial outflow, 650 ml. leaving the stomach in the first 10 minutes with the meal of 1,250 ml For the period between 10 and 40 minutes the rate of outflow of the meal of 750 ml. is greater than that for the meal of 1,250 ml. At 10 minutes the rate of outflow of the smallest meal of 330 ml. is greatest of all, but the smallest meal is technically unsatisfactory because the volume which may be recovered from the stomach after 20 to 30 minutes is sometimes too low to be estimated with precision These points were borne in mind when it was decided to use test-meals of 750 ml. to study the maximal emptying power of the stomach.

Further experiments have shown that meals given down a tube into the stomach empty more rapidly than similar meals swallowed in the ordinary way (Hunt, 1956), perhaps because the receptive relaxation of the stomach, which results from the movements of swallowing, is abolished (Cannon and Lieb,

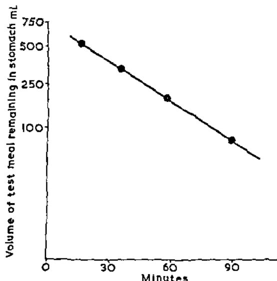


FIG. 2. The gastric emptying pattern for 750 ml. test-meal in a patient with a duodenal ulcer.

aorta per minute is probably at least a hundred times greater than the maximal volume entering the duodenum per minute.

A test of 'maximal' gastric emptying power

One question about gastric emptying which comes to mind is why does the stomach empty at different rates in different people? One possibility is that the rate of emptying depends simply upon the muscular strength or weakness of the stomach itself, a characteristic which might be assessed by determining the *maximal* rate at which the stomach can be made to empty.

The rate of emptying of the stomach at any moment may be regarded as a result of the interplay of stimulatory and inhibitory influences which together determine how much of the maximal emptying power shall work in driving the gastric contents into the duodenum. Thus to assess maximal emptying power by some functional test it is necessary to measure emptying whilst augmenting those influences which stimulate emptying and whilst eliminating as far as possible those stimuli which

maximal rate of emptying in 20 minutes is obtained for solutions of sodium bicarbonate and a slightly slower rate of emptying with solutions of sodium chloride at concentrations of about 120–200 milliosmols per litre. On the other hand meals with

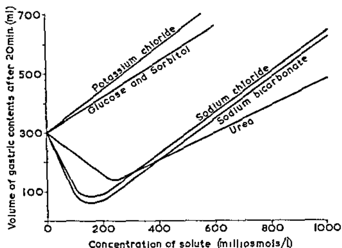


FIG. 4 The influence of the concentration of several solutes on the volume of gastric contents 20 minutes after taking a 750 ml. test-meal.

higher and lower concentrations of these solutes operate the duodenal brake so as to give slower rates of emptying as do all solutions of glucose, of sorbitol, and of potassium chloride. It is interesting to note that the relation between the concentration of urea, a unionized solute, and the rate of emptying is similar to the corresponding relationship for sodium salts. A detailed discussion of these data has been published elsewhere (Hunt, 1956) but they can be interpreted as indicating that alimentary receptors with a characteristic permeability and sensitive to osmotic pressure play a part in regulating gastric emptying. Of the solutes studied, sodium bicarbonate gives minimal inhibition of emptying but sodium bicarbonate is not as convenient as sodium chloride for inclusion in test-meals because it interferes with the simple estimation of the concentration of acid in the gastric contents Thus to determine the maximal gastric emptying power meals of 750 ml of a solution containing 200 milliosmols

1911), or because the stomach is filled more quickly by using the tube.

Having decided on the volume of the meal and a way of giving it which will hasten gastric emptying, there remains the

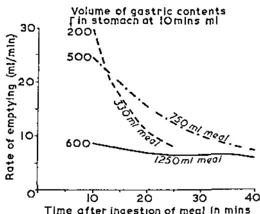


Fig. 3. The effect of the volume of meal ingested on the mean rate of emptying of the gastric contents (Hunt and Macdonald, 1954).

choice of its composition. Although the volume of the meal probably acts on gastric receptors to *stimulate* emptying the chemical constituents of the meal which *inhibit* emptying act very largely on extragastric receptors, which are mainly postpyloric. Fat and sugar inhibit emptying and therefore these ingredients ought to be avoided in any test-meal designed to study maximal emptying power.

To determine the solution which would activate to a minimal extent the postpyloric mechanism which inhibits gastric emptying a systematic study was made of the relation between the concentration of various solutes in test-meals and the rate of emptying of the meals. The detailed results of a series of experiments in one person are shown in Figure 4. The ordinate gives the volume of the gastric contents remaining 20 minutes after ingestion of the meal and the abscissa gives the concentrations of the various solutes expressed in milliosmols/l of meal so that equal numerical values correspond to equal osmotic pressures. It is clear that under the conditions of these experiments a

high osmotic pressure give more reproducible results than these test-meals containing 200 milliosmols NaCl/l. when the comparison is made in the same person.

The rapid emptying of the stomach which is believed to occur more frequently amongst patients with duodenal ulcer than

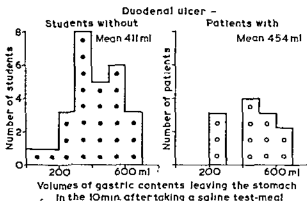


Fig. 5 Indices of 'maximal' gastric emptying power.

amongst normal persons, might be attributable to such patients having particularly muscular stomachs, a peculiarity which could perhaps be detected by comparing their 'maximal' emptying power with that of normal persons. Figure 5 also shows data on the volumes of the gastric contents which have left the stomach in the ten minutes after taking the saline test-meal for twelve patients with a diagnosis of duodenal ulcer. The means and the distribution of the two sets of data are almost identical which suggests that increased 'maximal' emptying power of the stomach is not the cause of any rapid gastric emptying which occurs in patients with duodenal ulcers.

The power of the duodenal brake

The rate of emptying of a meal containing a high concentration of glucose for example depends upon a balance between the 'maximal' emptying power and the opposing power of the duodenal brake which is applied as a result of the stimulation of receptors by the osmotic properties of the glucose If the duodenal brake were abnormally weak in patients with duodenal

of sodium chloride per litre have been used. In order to make reproducible observations it is desirable that the volume of the gastric contents should be 200 ml. or more at the time of the recovery. Experience with saline meals has shown that this is achieved by using a digestive period of 10 minutes. It must not be inferred that saline entering the duodenum has no inhibitory action on gastric emptying for it has been shown in the dog (Code and Watkinson, 1955) that a solution containing 200 milliosmols NaCl/l. injected into the duodenum at rates of about 5 ml./min. slows the emptying of a meal of meat. It follows therefore that the maximal rate of emptying assessed with a saline test-meal could probably be exceeded if it were possible to prevent the gastric effluent from stimulating postpyloric receptors. The finding that intragastric instillation of procaine increases the rate of gastric emptying (Roka and Lajtha, 1950) suggests a way in which the inhibitory action of the postpyloric receptors might be still further reduced.

Indices of 'maximal' emptying power for normal students and patients with duodenal ulcer

Figure 5 shows in the form of a frequency diagram for twenty-seven subjects the calculated values for the volume of gastric contents leaving the stomach in the 10 minutes after taking down a tube a 750 ml. test-meal containing phenol red as a marker and 200 milliosmols sodium chloride per litre. The method of calculation has been published (Hunt, 1954a). The volumes leaving the stomach shown on the abscissa vary widely from 55 ml. to 660 ml, a variation which presumably reflects the different 'maximal' emptying powers in these medical students. It is interesting to compare the very wide variation in these findings with the more homogeneous data of Figure 1 obtained when students were given test-meals containing 35 g. sucrose/l. It is clear from these and other data that the composition of test-meals can be varied to accentuate or minimize differences between individuals. It is generally found that in subjects with high emptying rates a standard stimulus to the duodenal brake is more effective in slowing emptying than it is in subjects with low emptying rates. It has also been found that test-meals of

responses. A solution containing 100 g. glucose/l. is not a maximal stimulus to the duodenal osmoreceptors but nevertheless it is sufficiently near to such a level to allow the response to be used as a tentative index of the maximal power of the duodenal brake.

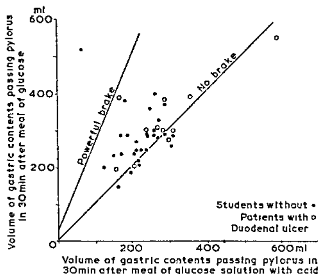


FIG. 7. The relation between the emptying of a test-meal of glucose solution (100 g /l.) and of glucose solution with acid (100 g. glucose and 20 m. equiv. HCl/l.).

The threshold of the duodenal brake for hydrochloric acid

The receptors for the duodenal brake are sensitive not only to the osmotic action of glucose but also to the action of hydrochloric acid. Because it seemed possible that rapid gastric emptying in patients with duodenal ulcer might result from the insensitivity of the duodenal receptors to low concentration of hydrochloric acid the change in gastric emptying produced by adding 20 m equiv. HCl/l. of test-meal of glucose solution (100 g./l.) was investigated. The results are shown in Figure 7 for normal students and eleven patients with duodenal ulcer. The ordinate gives the values for the volumes of gastric contents leaving the stomach after test-meals of glucose and the abscissa

ulcer it might be expected that meals of glucose solution would leave the stomach more quickly in such patients than in normal persons. Such an expectation would only be legitimate if the 'maximal' gastric emptying power were the same in the two groups of subjects as Figure 5 showed it to be.

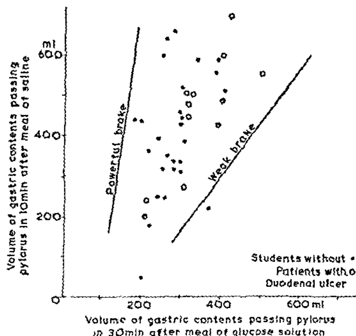


FIG 6. The relation between the emptying of a test-meal of glucose solution (100 g./l.) and of saline (100 m. equiv. NaCl/l.).

However a more sensitive test of this hypothesis could be made by comparing the volume of the gastric contents leaving the stomach after the saline meal with the volume of the gastric contents leaving the stomach after the meal of glucose solution in each individual. This comparison has been made in Figure 6 which shows the volume of the gastric contents leaving the stomach in 10 minutes with the saline meal, plotted against the volume of the gastric contents leaving in thirty minutes after the meal of glucose solution. It may be seen that the data for the students and for the patients with duodenal ulcers are so intermixed that the two groups cannot be distinguished by their

conclusions can only be accepted with all reserve since they do not take into account the degree of activity of the ulcer, the difference in the ages of the groups or the different degree of physical activity of the two groups at the time of the tests.

The use of saline test-meals for the investigation of slow gastric emptying

Patients having symptoms associated with very slow gastric emptying are often thought to have some mechanical obstruction to emptying at the pylorus or at the stoma after gastrectomy. The diagnosis is usually based on the history and an X-ray examination after a barium meal. The possibility that such slow emptying may result from a weak gastric musculature or from an unduly active duodenal brake is also worth consideration. A patient who had undergone gastrectomy complained of discomfort after eating for some weeks and had a considerable amount of barium in his stomach six hours after a barium meal. The surgeon was of the opinion that he had made the stoma too small. Nevertheless this subject emptied 400 ml. into his duodenum in twenty minutes when he was given a [illegible]

The influence of the viscosity of a test-meal on gastric emptying

It might reasonably be asked whether the study of the emptying of test-meals of very low viscosity is relevant to the emptying of ordinary food which gives a more viscous gastric content. However a comparison of the emptying of test-meals of sugar solution and sugar solution thickened with pectin to give a viscosity comparable to that of a thick motor oil showed that such a change in viscosity had no influence on gastric emptying or secretion (Hunt, 1954b)

Studies of Gastric Secretion

The importance of avoiding contamination

When measuring gastric secretory responses it is important to try to avoid contamination by secretions from the duodenum, mouth and oesophagus particularly in those instances where the

gives the values for the volumes leaving after test-meals of glucose and acid. Points which fall high and to the left indicate a powerful braking action in response to acid. There is no noticeable difference between the two groups in the slowing of gastric emptying produced by the acid.

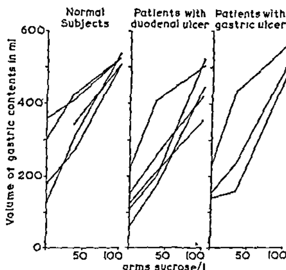


FIG 8. The volume of the gastric contents 30 minutes after taking 750 ml. test-meals containing 0, 35, and 100 g sucrose per litre (Hunt, 1954a).

Figure 8 shows the results of similar tests using sucrose to activate the duodenal brake which also failed to show any difference between patients with peptic ulcers and normal students. However there was a suggestion in the data that normal persons emptied meals of water less quickly than did the patients with duodenal ulcers (Hunt, 1954a)

From the unfinished experiments described above it may be tentatively concluded that the indices of 'maximal' emptying power of the stomach and of the power of the osmotic brake are not noticeably different in a group of patients with the diagnosis of duodenal ulcer from the indices found in a group of medical students. There is a suggestion that there may be a difference between the responses of the osmotic receptors of the duodenal brake mechanisms of the two groups for test-meals of water which provide a relatively small stimulus to the receptors. These

it is clear that the points lie closer to a curved line than to the straight line required by the two-component hypothesis. It seems unlikely that this divergence from the straight line predicted by the two-component hypothesis can be accounted for

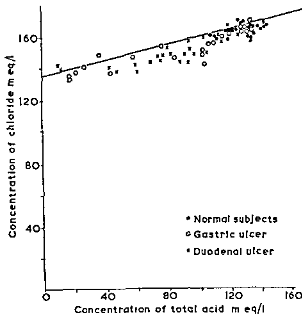


FIG 9. Concentration of total acid plotted against concentration of chloride (Ihre, 1938) in gastric secretion

by contamination from extragastric sources for there is a similar divergence in the data of Gudiksen (1950) for feline gastric secretion which was collected without the possibility of contamination This curvilinear relationship between the concentration of acid and chloride in gastric secretion has not received much emphasis before except by Ihre (1938) (see also Heinz and Obrink, 1954), possibly because the data which were least open to objection, obtained from experiments on dogs with gastric pouches, did not cover a sufficiently wide range of acidities to make the curvilinear relationship obvious. There is further data at variance with the original two-component hypothesis in some work quoted in Table 3 by kind permission of Dr. A. Gilman

rate of gastric secretion is low. In such circumstances even a small volume of these contaminants, which may all contain bicarbonate on occasion, will significantly alter the composition of the recovered secretions. This point makes it desirable to apply powerful excitatory stimuli to the gastric glands whenever this is feasible so as to minimize the effect of contamination from extragastric sources.

Variations in the concentration of inorganic ions in gastric secretion

The variations in the concentration of acid and chloride in human gastric secretion collected by Ihre (1938) are shown in Figure 9. As the concentration of acid rises so does the concentration of chloride but to a very much less degree. One hypothesis set up by Hollander (1938) to account for these variations postulates that the gastric secretion is a mixture of two parts.

TABLE 2. The composition of the hypothetical parietal component and non-parietal secretions in man

milliequivalents/l.			
Parietal		Non-parietal	
H^+ 160	Cl^- 170	Na^+ 160	Cl^- 125
K^+ 10		K^+ 10	HCO_3^- 45
170	170	170	170

The parietal component is thought to issue only from the parietal cells but the non-parietal secretions are a mixture of the inorganic external products of all the other types of cell of the gastric mucosa, both fundic and antral. A composition suggested by Fisher and Hunt (1950) for these two parts for man based on the data of Ihre (1938) is shown in Table 2. Although the non-parietal secretions are assumed to have a virtually constant composition this is unlikely to be so under special conditions of stimulation. If varying proportions of the two hypothetical components shown in Table 2 are mixed a plot of the concentration of chloride against the concentration of acid in each mixture will lie on the straight line shown in Figure 9. The fit of the experimental points to the line in Figure 9 is an indication of the success of the hypothesis in accounting for the data. However

of the amounts of chloride and acid in the secretion. The relationship shown in Figure 10 is used to determine the volume of parietal secretion in the data presented later in this lecture.

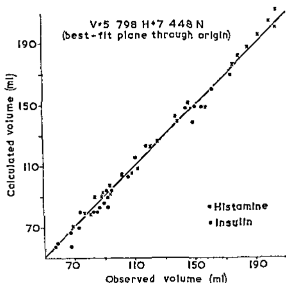


FIG. 10. Comparisons of calculated and observed volumes of gastric juice (Fisher and Hunt, 1950).

The two-component hypothesis has an important consequence. A neutral gastric juice is one in which the parietal component is exactly neutralized by the non-parietal secretions so that a neutral gastric juice does not correspond to zero parietal activity.

The volumes of the hypothetical parietal component and non-parietal secretions in a sample of gastric juice can readily be calculated from the amounts of acid and chloride recovered (Hunt, 1954a) The data so obtained for the parietal component are probably better indices of parietal activity than the amounts of acid recovered. The data for non-parietal secretions are to be treated with reserve on theoretical grounds and are sometimes found to be unreliable in practice because they are specially subject to the influence of contamination by extragastric secretions. However, provided these reservations are kept in mind the

from his Ph.D. thesis (1931). It may be seen that at the beginning of experiments in which the gastric secretion from Heidenhain pouches in dogs was collected there was a considerable rise in the concentration of acid without any change in the concentration of chloride. These data are in harmony with the original Rosemann hypothesis (1907) that the concentration of chloride is constant whilst the concentration of acid varies. A modern

TABLE 3. Concentrations of acid and chloride in canine gastric juice (m. equiv./l.) (Gilman, 1931)

Period	Conc. H^+	Conc. Cl^-
1	125 6	170 4
2	134 0	164 0
3	142 0	164 8
4	142·4	165 2
5	142 0	164 2
1	96 8	162 0
2	121 2	160 0
3	134 0	160 0
4	134 0	160 0

extension of the Rosemann hypothesis is given by Heinz and Obrink (1954). These data which do not fit in with the hypothesis that the gastric secretion may be considered as a mixture of two components of virtually constant composition have been presented in order that the limitations of the working hypothesis may be recognized, but such divergent data are uncommon in the literature. For the most part the two-component hypothesis accounts reasonably well for the relationship between the amounts of acid and chloride secreted and the volume of the secretion. This may be seen in Figure 10 based on Ihre's data (1938) in which the measured volume of secretion is contrasted with the volume calculated from the amounts of acid and chloride in the secretion by substituting in the relation

Volume = 5 798 (amount of acid)
+7·448 (amount of neutral chloride) expressed in m. equiv.

Some of the agreement should however be recognized as resulting from the value for volume inevitably appearing in the calculation

component as patients without ulcers. The data of Kay from Glasgow (Hunt and Kay, 1954) show a similar difference between the two groups for the diurnal basal secretion of parietal component. In our present state of knowledge it is reasonable to assume that in those patients who have such gastric hypersecretion it provides for a duodenal ulcer an unfavourable environment which retards healing and it is therefore a matter of some clinical interest (Atkinson and Henley, 1955). It now remains to frame and test some hypotheses which might account for this hypersecretion under basal conditions.

The mechanism of the regulation gastric secretion

The gastric secretory mechanism may be considered to have the three parts of a reflex arc, (1) receptors of stimuli which ultimately activate the secretory cells of the mucosa, (2) the peripheral effectors, e.g. the parietal cells, and (3) the connexions, either nervous or hormonal, between the receptors and the effectors. When there is some quantitative abnormality of secretion the fault may lie in the working of one or several of these three parts. Thus one type of analysis of the hypersecretion of patients with duodenal ulcers can be resolved into determining *the degrees of reactivity of the receptors and effectors*, an idea which is illustrated in the following series of figures. Figure 11*a* represents the postulated reactivity of these parts of the reflex arc in a normal person. A standard stimulus impinges on the receptor which fires one unit of stimulation into the gastric mucosa which forms one unit of secretion. Figure 11*b* shows an abnormal arc in which a doubly reactive receptor fires two units of stimulation in response to the standard stimulus so that the secretory response is twice normal. In 11*c* the receptor is represented as normally reactive but the doubly reactive mucosa now forms two units of secretion in response to the standard stimulus. Figure 11*d* shows a combination of a doubly reactive receptor acting on a doubly reactive secretory mechanism with *the resulting 4 units of secretion* A *normal* response from an abnormal mechanism where the doubly reactive receptor operates a half reactive mucosa is shown in Figure 11*e*.

concepts of parietal component and non-parietal secretions are a convenience in thinking about gastric secretory activity. Moreover, when the hypothesis is superseded, data reported in terms of the parietal and non-parietal secretions can readily be converted back into amounts of acid and chloride.

An Analysis of the Gastric Hypersecretion of Acid by Patients with Duodenal Ulcer

The basal secretion

It is now widely agreed that under basal conditions the diurnal and nocturnal secretion of acid by patients with duodenal ulcer is greater in amount than that of persons without duodenal ulcer.

Table 4. The mean volumes of parietal component in the nocturnal secretion of patients with and without duodenal ulcer (Levin, Kirsner, Palmer and Butler, 1948)

Subjects' condition	Number of studies	Mean volume of parietal component (ml.)	Standard error of mean
WITHOUT duodenal ulcer	33	240	±22
WITH duodenal ulcer	72	526	±29

The majority of workers who have measured basal secretion have presented their data in terms of the amounts of acid recovered. Reasons have been given above for thinking that the amount of acid recovered may not be the best index of the secretory activity of the parietal cells so that in this presentation the data of other workers have been transformed into volumes of parietal secretion, which is assumed for the moment to contain 160 m. equiv. H^+/l. and 170 m. equiv. Cl^-/l. (Thompson and Vane, 1953). A study of Ihre's data (1938) has shown that these values are applicable to the gastric secretion of patients with peptic ulcers (Hunt, 1951a).

Table 4 shows some data for nocturnal secretion taken from the literature. It may be seen that as a group patients with duodenal ulcers secreted more than twice as much parietal

patients with duodenal ulcer secreted about 30 per cent more parietal component than the selected normal persons in response to a body-weight dose of histamine (0·1 mgm histamine acid phosphate/10 Kg. body-weight). If the sole difference between patients with duodenal ulcer and these normal persons lay in the reactivity of the peripheral parietal secretory mechanism it

TABLE 5. Volumes of acid component secreted in response to histamine and insulin (Ihre, 1938; Hunt, 1950a)

	Normal	Patients with	
		Gastric ulcers	Duodenal ulcers
Number of subjects	18	17	13
Histamine (ml.)	91·6	82·4	119·6
Standard error of mean	±7·1	±13·1	±13·1
Insulin (ml.)	118·7	102·7	145·8
Standard error of mean	±9·5	±14·7	±17·0

would be expected that the patients would secrete 30 per cent more parietal component than these normal persons in response to any standard stimulus. Insulin, which stimulates gastric secretion via the vagus as a result of the action of hypoglycaemia on cephalic receptors, was also used by Ihre in these two groups of subjects. Table 5 also shows that the patients with duodenal ulcer actually secreted 23 per cent more parietal component than the normal persons in response to a standard stimulus with insulin but this figure is not significantly different from the expected 30 per cent. Thus these data of Ihre taken at their face value indicate that the hypersecretion of patients with duodenal ulcer in response to insulin can be accounted for by the increased peripheral parietal reactivity demonstrated in the response to histamine.

This type of analysis would be more convincing if it were possible to assess the maximal secretory power of the gastric mucosa. Thanks to the work of Kay (1953) this is now possible.

A test of maximal parietal secretory power

Large doses of histamine are noxious but their effects can be made tolerable by adequate doses of mepyramine maleate

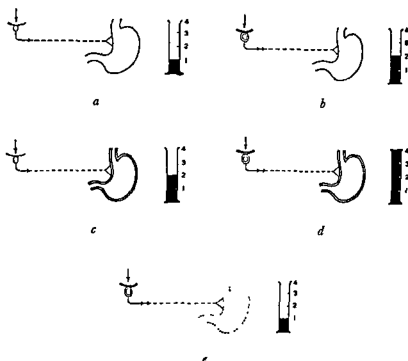


FIG. 11*a* A normal arc.
b. An arc with a doubly reactive receptor.
c. An arc with a doubly reactive mucosa.
d. An arc with a doubly reactive receptor and mucosa.
e. An arc with a doubly reactive receptor and a half reactive mucosa

The assessment of parietal secretory power

The first question to be asked is, Does an abnormally high secretory power of the gastric mucosa account for the hypersecretion of duodenal ulcer? To answer this requires some test which will give an index of parietal secretory power. Histamine seems to be a suitable stimulus for use in such a test since it acts on the parietal cell even in a transplanted gastric pouch of gastric mucosa without Auerbach's plexus (Klein, 1932). Table 5 allows a comparison of the secretory responses of selected normal young men with those of male patients with duodenal ulcer based on the data of Ihre (1938). It may be seen that the

patients with duodenal ulcer secreted about 30 per cent more parietal component than the selected normal persons in response to a body-weight dose of histamine (0·1 mgm. histamine acid phosphate/10 Kg. body-weight). If the sole difference between patients with duodenal ulcer and these normal persons lay in the reactivity of the peripheral parietal secretory mechanism it

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Number of subjects	18	17	13
Histamine (ml)	91 6	82 4	119 6
Standard error of mean	±7 1	±13 1	±13 1
Insulin (ml.)	118 7	102 7	145 8
Standard error of mean	±9 5	±14 7	±17 0

would be expected that the patients would secrete 30 per cent more parietal component than these normal persons in response to any standard stimulus. Insulin, which stimulates gastric secretion via the vagus as a result of the action of hypoglycaemia on cephalic receptors, was also used by Ihre in these two groups of subjects Table 5 also shows that the patients with duodenal ulcer actually secreted 23 per cent more parietal component than the normal persons in response to a standard stimulus with insulin but this figure is not significantly different from the expected 30 per cent. Thus these data of Ihre taken at their face value indicate that the hypersecretion of patients with duodenal ulcer in response to insulin can be accounted for by the increased peripheral parietal reactivity demonstrated in the response to histamine.

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A test of maximal parietal secretory power

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(Anthisan) which do not block the stimulating action of histamine on the parietal cells. In Kay's augmented histamine test he first collects the basal secretion and then determines the secretory response to a dose of histamine which is known to

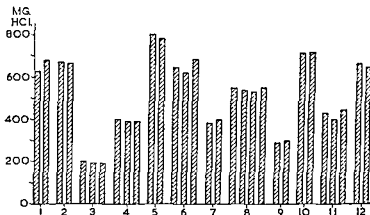


Fig. 12. Gastric HCl output after histamine (4 B.W. doses). Repeated estimations in 12 patients. Mgm./30 minutes (Kay, 1953).

produce a maximal gastric secretory response in the presence of a protecting dose of mepyramine maleate. Figure 12 shows that using this large dose of histamine on several occasions gives very reproducible secretory responses. This test was used to assess the 'maximal' secretory power of patients without duodenal ulcer and of patients with duodenal ulcer. It may be seen in Table 6 that in the patients with duodenal ulcer, who were candidates for gastrectomy in Glasgow, the mean output of parietal component in 45 minutes after a maximal dose of histamine was 135 ml. as compared with 86 ml. in the control subjects under *the same conditions. There was therefore a significantly increased* 'maximal' parietal secretory power in these patients with duodenal ulcer. These data of Kay probably give a better index of the magnitude of the abnormality in patients with duodenal ulcer than do those of Ihre (1938) because the control subjects of Kay's data were of about the same age and weight as the patients with duodenal ulcer, whereas Ihre's data were for selected young men. Thus Figure 11*c* describes more or less

quantitatively the state of the parietal secretory arc in patients with duodenal ulcer. The gastric responses to large doses of histamine are maximal for histamine but this does not necessarily mean that no higher rate of secretion is possible. However,

TABLE 6. Data on the secretion of parietal component by normal persons and patients with duodenal ulcer (ml /30 min.)

	Male normal persons	Male patients with duodenal ulcer		
		No stenosis	Moderate stenosis	Severe stenosis
Number of persons	27	81	42	29
Mean basal secretion of parietal component	15·7	33 8	46 0	39 8
Standard error of mean	±1·7	±2 5	±5 3	±4 6
Mean maximal parietal response to histamine	86 0	135 3	165 1	160 4
Standard error of mean	±9 6	±7 1	±9 7	±10 1
Mean weight (kg.)	60 8	58 5	58 0	53 0
Standard error of mean	±1 8	±1 0	±1·1	±1 0
Mean age (years)	44 1	38 3	42 9	49 1
Standard error of mean	±2 5	±1 0	±1 6	±1 4
Mean duration of symptoms (years)	—	13 1	15 0	17 2
Standard error of mean	—	±0 9	±1 3	±1 6

it is difficult to imagine any set of conditions likely to evoke a greater response, for not only is the stimulus to secretion large but by aspirating the secretion the possibility of inhibitory effects operating from the duodenum is minimized.

The significance of the dose response relationship for histamine

The hypothesis developed above suggests that a high maximal response to histamine will be associated with a mucosa which will give a high response to any form of stimulus bearing on the parietal cells.

It could be objected that patients with duodenal ulcer might have a number of parietal cells with a high threshold for stimulation which would respond to large doses of histamine but not to stimuli of normal physiological quality If this were so the high maximal parietal secretory power in such patients might

(Anthisan) *which do not block the stimulating* action of histamine on the parietal cells. In Kay's augmented histamine test he first collects the basal secretion and then determines the *secretory response to a dose of histamine* which is known to

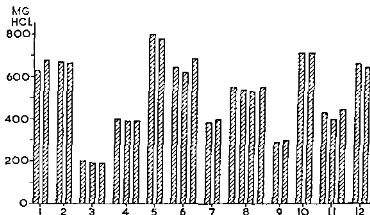


FIG. 12. Gastric HCl output after histamine (4 B.W. doses). *Repeated estimations in 12 patients. Mgm /30 minutes (Kay, 1953).*

produce a maximal gastric secretory response in the presence of a protecting dose of mepyramine maleate. Figure 12 shows that using this large dose of histamine on several occasions gives very reproducible secretory responses. This test was used to assess the 'maximal' secretory power of patients without duodenal ulcer and of patients with duodenal ulcer. It may be seen in Table 6 that in the patients with duodenal ulcer, who were candidates for gastrectomy in Glasgow, the mean output of parietal component in 45 minutes after a maximal dose of histamine was 135 ml. as compared with 86 ml in the control subjects under the same conditions There was therefore a significantly increased 'maximal' parietal secretory power in these patients with duodenal ulcer. These data of Kay probably give a better index of the magnitude of the abnormality in patients with duodenal ulcer than do those of Ihre (1938) because the control subjects of Kay's data were of about the same age and weight as the patients with duodenal ulcer, whereas Ihre's data were for selected young men. Thus Figure 11*c* describes more or less

out of six trials if there were in fact no difference between the two groups in this respect. These figures suggest that the increased diurnal basal secretion in patients with duodenal ulcer can be almost wholly accounted for on the assumption that a

TABLE 7. Percentage of the maximal secretory power active in basal secretion

	Male normal persons	Male patients with duodenal ulcer			
		No stenosis	Moderate stenosis	Severe stenosis	All
Mean ratio:					
$\frac{\text{Basal parietal secretion} \times 100}{\text{Maximal parietal response to histamine}}$	22 4	25 6	26 7	25 4	25 9
Standard error of mean ratio	±2 2	±1·3	±2 0	±2 3	±0 95

normal degree of stimulation is bearing on a peripheral effector of nearly twice the normal power. It thus becomes unnecessary to postulate that the pathways in the vagus mediating the cephalic phase of secretion are overactive. Those who favour this concept of vagal overactivity can point out that the nocturnal basal secretion in patients with duodenal ulcers is much reduced by vagotomy and that the basal secretion must have been the result of activity in vagal secretory fibres. Table 8 shows some data derived from a publication by Dragstedt (1952), which allow the volume of parietal component recovered during the night to be calculated. It is clear that after vagotomy the recovery fell by about 67 per cent. However, data from the same group of workers show that the secretory response to histamine fell by 75 per cent after vagotomy. Assuming that the change in the response to histamine is proportional to the change in the reactivity of the parietal secretory mechanism, the actual fall in the basal output of parietal component was slightly less than would be expected had the stimulus bearing on the parietal cells remained unchanged. If it were permissible to follow this argument to its conclusion it would seem that no vagal secretory, as distinct from trophic, fibres are active in

not account for their high basal secretion of acid. However, examination of the relation between the percentage of the 'maximal' secretory power activated by a given dose of histamine in normal persons and patients with duodenal ulcers

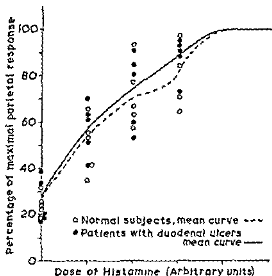


FIG 13 Relation between dose of histamine and parietal response (*Hunt and Kay, 1954*).

given in Figure 13 shows that this objection cannot be sustained since the mean curves for five patients without duodenal ulcer and five patients with duodenal ulcer are almost identical.

The proportion of the 'maximal' secretory power active under basal conditions

Although the maximal parietal response to histamine may not be the true maximal parietal secretory power the response may be assumed to provide a useful index of the maximum. It now becomes possible to ask a new question. What percentage of the maximal secretory power is active under basal conditions in patients without duodenal ulcer and patients with duodenal ulcer? Table 7 shows that 22 per cent of the 'maximal' capacity is active in normal persons and 26 per cent in patients with duodenal ulcer. Such a difference would arise by chance once

found. These results can be accounted for by supposing that stenosis will increase gastric distension which is known to be a stimulus to secretion (Hunt and Macdonald, 1952; Macdonald and Spurrell, 1953), and that the increased parietal secretory power corresponds to a work hyperplasia of the parietal cells. There is some evidence that work hyperplasia can be produced in the stomach, for Friedman (1953) found that the weight of the stomach increased in mice when the bulk of their diet was increased by undigestible material, and Cox and Barnes (1945) reported an increase in the number of parietal cells in guinea-pigs given injections of histamine in beeswax for three weeks. This has been confirmed in dogs by Tongen (1950).

There is evidence which suggests that variation in the parietal responses to standard stimuli amongst normal subjects as well as the difference between the responses of normal subjects and patients with duodenal ulcer can be to a large extent accounted for by the varying parietal secretory power of different normal subjects, for the secretory responses to test-meals, to insulin and to basal conditions are all correlated with the response to histamine (Hunt, 1950b).

The inhibition of gastric secretion

The rate of parietal secretion at any moment depends upon the balance between stimulation and inhibition bearing on the mucosa. Quantitative intersubject comparisons of the secretory inhibition produced by standard stimuli are therefore essential for understanding this balance.

The two tests which have most convincingly brought out the difference between patients with duodenal ulcer and normal persons were the augmented histamine test of Kay and measurements of basal secretion, both of which reflect mainly the increased peripheral reactivity. Unpublished studies of the secretory responses to saline test-meals at Guy's Hospital show that the parietal secretory response is about twice as great in patients with duodenal ulcer as it is in normal persons. The mean amount of acid secreted in response to a 750 ml saline meal of ten minutes' duration by a group of twenty-seven medical students was 2·6 m. equiv. (S.E. of mean ± 0 3) as compared with

basal secretion in patients with duodenal ulcer: had such fibres been active the fall in the output of parietal secretion would have been more than the 75 per cent which can be accounted for on the basis of the reduction in peripheral reactivity as assessed with histamine.

TABLE 8. The mean volumes of parietal component secreted in response to basal conditions and in response to histamine, before and after vagotomy (Dragstedt, 1952; Oberhelman and Dragstedt, 1948)

Number of patients	Condition	Vol. of parietal component (ml.) basal secretion per 12 hours	Reduction after vagotomy
135	Duodenal ulcer prevagotomy	514	
70	Duodenal ulcer postvagotomy	170	67%
	Secretion stimulated by histamine		
18	Peptic ulcer prevagotomy	185	
18	Peptic ulcer postvagotomy	47	75%

It seems probable at the moment that the increased 'maximal' parietal secretory power found in patients with duodenal ulcers is the result of an increased number of parietal cells in the gastric mucosa of such patients, for Cox (1952) has found that male patients with duodenal ulcer have 75 per cent more parietal cells than male patients without ulcer, whilst Kay's figures show that such patients have a maximal parietal secretory power 72 per cent greater than normal persons. The factors which determine the number and reactivity of the parietal cells in the gastric mucosa appear to be of fundamental importance for the understanding of the hypersecretion of parietal component by patients with duodenal ulcer.

There are probably a number of influences regulating the parietal secretory power. In the analysis of Hunt and Kay (1954) it was found that amongst patients with pyloric stenosis at the time of their gastrectomy the 'maximal' parietal secretory power increased with the duration of the dyspepsia whereas in the other patients without stenosis no such correlation was

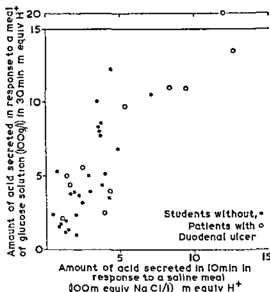


FIG. 14. A comparison of the secretory responses to meals of gucose solution (100 g./l.) and of saline (100 m. equiv. NaCl/l.).

The inhibition of secretion by the acid in the gastric contents

During the augmented histamine test the whole of the gastric secretion is withdrawn so that there can be no possibility of the secreted acid acting on receptors which might inhibit the gastric secretory response. On the other hand when a test-meal is used as a stimulus, the greater the secretion of acid the more acidic will be the gastric contents and the greater will be the probability of the inhibition of secretion by the action of the gastric contents on duodenal and possibly antral receptors (Woodward, Lyon, Landor and Dragstedt, 1954). Shay (1944) has suggested that the hypersecretion of acid by patients with duodenal ulcer depends upon the failure of the duodenal mechanism to inhibit secretion because its threshold is raised. It was therefore decided to determine the response to the addition of acid to a test-meal given to normal students and to patients with duodenal ulcer

The choice of the composition of the control test-meal in

5·25 m. equiv. (S.E. of mean ±1·0) secreted by eleven patients with the diagnosis of duodenal ulcer. The data are not expressed in terms of parietal component because the meals contained large amounts of chloride which makes the estimation of parietal component less reliable than usual. This particular set of data has been chosen because there is presumably a minimal possibility of the inhibition of secretion by the gastric contents acting on duodenal receptors since the meal itself probably has little inhibitory action and in ten minutes the acidity of the gastric contents does not reach levels which are thought to activate the duodenal and possibly the antral receptor mechanisms which inhibit secretion (Woodward, Lyon, Landor and Dragstedt, 1954). T'
test-meals cor
much more s
period of thirty minues was practicable. The mean responses were 34·4 ml. (S.E. of mean ±3·4) of parietal component for the medical students and 62 ml. (S.E. of mean ±9·8) for the eleven patients with the diagnosis of duodenal ulcer. From these data it appears that whether or not the test conditions activate inhibitory receptors the mean total response in these patients with duodenal ulcers is about twice that in normal students, a finding which could be accounted for on the basis that such patients have as a group about twice as many parietal cells as these normal subjects.

There is a further possibility that if patients with duodenal ulcers have a relatively weak osmotic brake restraining secretion, it might only be detected by a more sensitive test. In Figure 14 the amount of acid secreted in response to the saline meal in ten minutes has been plotted against the amount secreted in thirty minutes after the meal of glucose solution. The saline meal presumably activates the inhibitory mechanism to a minimal degree whilst the glucose solution is a powerful activator of the mechanism. It may be seen in Figure 14 that the points for patients with duodenal ulcer are freely intermixed with those for the medical students so that presumably the osmotic brake on secretion is of about equal power in the patients with duodenal ulcer and the medical students.

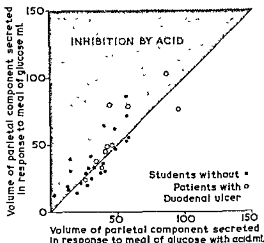


Fig. 15. Parietal secretion in 30 minutes after test-meal of glucose solution (100 g /l.) and glucose solution with acid (100 g /l + 20 m equiv. HCl/l.).

Conclusion

The possibility that a high gastric secretion in normal persons and in patients with duodenal ulcer may be accounted for by special features in *several* parts of the regulating mechanism is worth consideration The hypersecretion which occurs in some patients with duodenal ulcers could then be regarded as an extension of one end of the normal range, rather as patients with

lower blood pressures (Miall and Oldham, 1955) Such a hypothesis allows for the interaction of hereditary and environmental factors for it is known that very remarkable changes in gastric secretion may accompany change in the circumstances of life (Hunt, 1951b).

SUMMARY

To give a simple, probably unduly simple, summary of the abnormalities of gastric secretion in patients with duodenal ulcer, it may be said that the mean parietal secretory power is

which the acid must be incorporated is important in interpreting the results. Most stimuli which inhibit gastric secretion simultaneously slow gastric emptying. But slowing of gastric emptying gives an increased distension stimulus to the stomach so that the inhibitory action of the meal may be more than counterbalanced by the increased stimulus to secretion. Such a relationship between the inhibitory and stimulatory effect of increasing concentrations of sucrose has been found in two normal subjects (Hunt, 1954a). These points were borne in mind when it was decided to use test-meals containing 100 g. glucose/l. and 100 g. glucose plus 20 m. equiv. HCl/l. to determine the effect of acid in a test-meal on the resulting gastric secretion. It was anticipated that the addition of acid to a glucose solution would make little difference to the rate of emptying with the result that the stimulus to secretion would be substantially unchanged.

Figure 15 shows on the ordinate the volume of parietal component secreted in response to the meal of glucose solution (100 g./l.) and on the abscissa the amount of parietal component secreted in response to a meal of the same solution with 20 m. equiv. HCl added per litre of meal. It is clear that the data for normal persons and patients with duodenal ulcer are freely intermixed and that there is no noticeable difference between the two groups. Since there are approximately twice as many points for subjects showing inhibition of parietal secretion as there are for persons showing no inhibition it is clear that 20 m. equiv. HCl/l. is a suprathreshold stimulus for the inhibitory mechanism. However, in one patient with duodenal ulcer with marked hypersecretion the addition of acid to the meal was followed by an increase in secretion of parietal component.

In general the greater is the secretory response of the stomach, the more readily is it inhibited by such a stimulus as high concentrations of sucrose (Hunt, Macdonald and Spurrell, 1951.) The finding that in the two patients mentioned above the addition of 20 m. equiv. HCl/l. of meal failed to inhibit secretion is therefore of some interest. It confirms the hypothesis of Shay (1944) with the implication that failure of autoregulation of gastric secretion is a possible cause of hypersecretion but not the sole cause.

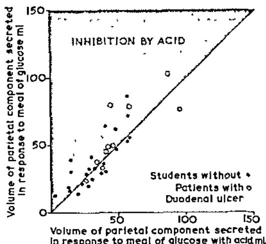


Fig. 15. Parietal secretion in 30 minutes after test-meal of glucose solution (100 g./l.) and glucose solution with acid (100 g /l. + 20 m. equiv. HCl/l.).

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lower blood pressures (Miall and Oldham, 1955). Such a hypothesis allows for the interaction of hereditary and environmental factors for it is known that very remarkable changes in gastric secretion may accompany change in the circumstances of life (Hunt, 1951b).

Summary

To give a simple, probably unduly simple, summary of the abnormalities of gastric secretion in patients with duodenal ulcer, it may be said that the mean parietal secretory power is

about double that of normal persons and this can account for the observed hypersecretion under basal conditions and after stimulation with test-meals.

In some patients there is in addition a failure of the autoregulation of gastric secretion as shown by Shay.

ACKNOWLEDGEMENTS

Much of the work referred to was done with Professor W. R. Spurrell and Dr. I. Macdonald at Guy's Hospital and with Mr. A. Kay, F.R.C.S., of Glasgow. It is a pleasure to thank many clinical colleagues for permission to investigate their patients with peptic ulcers, the patients themselves and the students who have cooperated in these studies.

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XXI

The Treatment of Hepatic Coma

J. F. STOKES

HEPATIC coma is not a common condition and is capable of unpredictable and spontaneous recovery; these two facts make it extremely difficult to judge the effect of treatment and give rise to contradictory and confusing reports. The position is still worsened by lack of precision in the definition of 'hepatic coma'; various kinds of coma plus jaundice or coma plus enlarged liver may be collected together in an attempt to provide a series of cases on which the effects of treatment may be judged, and the fact that severe electrolyte disturbance and cerebral manifestations of thiamine deficiency are not uncommon in cirrhotics may be overlooked. Recently, too, the clinical pattern of illness produced by viral infection has become less clear-cut; this influences the problem in that coma due to encephalomyelitis may be present together with clinical and biochemical evidence of impaired liver function Comparison between series is further complicated by the fact that hepatic coma is notoriously more difficult to influence when it occurs in association with acute liver disease than with cirrhosis.

The forty-five cases Miller and I reported in 1947 (Stokes and Miller, 1947) were all in coma as a result of acute hepatitis caused by a particularly virulent virus. All but one of these died; but they cannot be used as a yardstick by which to measure the progress we have made in treatment, since any current series is likely to include a high proportion of comatose cirrhotics, in whose state, as we shall see, certain temporary modifications can be made.

Though hepatic coma seems at first sight an unpromising

subject to discuss here, there is no doubt that our understanding of the condition has increased in the last decade and, encouraged by the belief that these lectures are designed to provoke rather than instruct, I want to use this opportunity to see what can be learned from forty-seven cases of hepatic coma which were observed at University College Hospital or in my private practice between 1948 and 1955. The material from which I am arguing is shown in Tables 1 and 2.

TABLE 1. Hepatic coma, 1948–55

	Cases	Died	Recovered
Acute hepatitis	8	8	0
Subacute hepatitis	8	8	0
Cirrhosis	31	28	3

TABLE 2. Cirrhosis in hepatic coma, 1948–55

	Cases	Died	Recovered
Alcoholic	11	10	1
Cause obscure	10	9	1
Post-hepatitic	6	5	1
Ulcerative colitis	2	2	0
Biliary	1	1	0
Haemochromatosis	1	1	0

It will be seen that we have had no striking success in saving these people's lives, but I should say that among the group of thirty-one cirrhotics we can add nine episodes of coma occurring in eight patients between one and twenty-two months before death, making a total of twelve attacks of coma followed by recovery, either spontaneous or consequential to treatment. I would emphasize that these all occurred in cirrhotic patients, and were preceded by gastro-intestinal haemorrhage in four instances. No case of acute hepatitis survived coma.

The position in regard to treatment at the beginning of this series of cases was that I was convinced of two things in the light of experience of hepatic coma in Burma. Firstly, I was convinced of the danger of giving normal doses of morphine or barbiturates to patients in the active and sometimes violent phase of coma; liver failure allows of the continued action of

these drugs which remain unchanged in the body tissues and may tip the balance against the patient by prolonging coma and depressing respiration. Paraldehyde is the only safe drug to use if the violence of coma interferes with treatment. Secondly, I was convinced of the value of parenteral vitamin K, which might limit haemorrhage not only into the gut but also into the liver itself and so prevent further hepatocellular damage; gastro-intestinal haemorrhage is, as we shall see, of importance in the comatose cirrhotic, while bleeding into the liver is of greater consequence in cases of fulminant hepatitis.

Protein and Ammonia

The value of protein treatment, however, seemed to be questionable. Enthusiasm derived from occasional Sunday morning feeding of Himsworth's rats was modified by awareness of the syndrome of meat intoxication in dogs. I feel sure, in retrospect, that uncertainty on this point brought about the deaths of two of my patients, who were fed protein vigorously as soon as they emerged from coma, and had to lapse back into unconsciousness before they could escape the deleterious effects of treatment.

The present position of protein in the therapy of hepatic coma is clear. It must be avoided. The forced feeding of meat to dogs with an Eck fistula has been known since 1893 (Hahn, Massen, Nencki and Pavlov) to produce neurological damage, and varying explanations have been offered to account for this (Magnus-Alsleben, 1920; Fuchs, 1921; Svec and Freeman, 1949). Burchi in 1927 observed high blood ammonia levels in cirrhosis, and van Caulaert and Deviller (1932), and Fuld (1933), found that ammonium salts were capable of producing coma and high blood levels in cirrhotics Here the matter rested until 1952 when interest was reawakened by Phillips, Schwarz, Gabuzda and Davidson reporting the production of hepatic coma in cirrhotics by feeding various nitrogenous substances. Since then, different degrees of neurological disorder from full coma through 'episodic stupor' to spasticity and tremor have been repeatedly brought about in some cirrhotics by feeding high protein diets, by giving ammonium salts or ion-exchange resins in the ammonium phase (Gabuzda, Phillips and Davidson, 1952).

These findings have been confirmed in this series. They provide difficulties in treating ascitic and diabetic patients. These can be overcome easily in the former by avoiding ammonium-containing medicines; but the adjustment of the protein-carbohydrate balance of the diet in haemochromatosis is awkward on account of the insulin resistance so often encountered.

These neurological changes have been correlated with high levels of ammonia in the systemic blood (Riddell, Kopple and McDermott, 1954; McDermott, Adams and Riddell, 1955), and the view that these levels are achieved by direct access of ammonia from the gut to the systemic veins via a network of venous collateral channels developed in response to portal hypertension (Sherlock, Summerskill, White and Phear, 1954) receives support from two observations; first, the appearance of coma and increase in blood ammonia as a result of porta-caval shunt operations, and second, the demonstration of high blood ammonia levels in cirrhotics whose liver function is reasonably good.

There is a paucity of observations on ammonia levels in acute hepatitis. Kirk (1936) reports them as normal, but he was not dealing with comatose cases, and one of Riddell and McDermott's (1954) cases, in coma as a result of acute hepatitis, had a distinctly high level, and this can only have been the result of hepatocellular failure.

There is, however, a certain lack of correlation between blood ammonia levels and coma in some cases (Singh, Barclay and Cooke, 1954). Though most patients in coma will usually show a high reading, Summerskill (1955) found two out of twenty-nine cases with normal levels, and Eiseman (discussing McDermott, Adams and Riddell, 1954) found normal levels in 'about half' his cases of hepatic coma.

Consciousness may be maintained, too, in the face of blood ammonia levels which, in another person, would be associated with deep coma, in this context, however, it is difficult to avoid comparison with uraemia, in which the level of consciousness depends more on the speed of accumulation of urea in the blood than on the absolute reading.

Those who are familiar with the recent vicissitudes of Professor Quatermass's associates will have realized the popular

appeal of ammonia as a substance capable of producing neuro-psychological disorder, and the ammonia story as a whole carries some conviction, though I do not think it can provide a complete explanation of hepatic coma. It bears on treatment not only in the prophylaxis of coma by giving a low protein diet and avoiding ammonium-containing medicines in patients with a dangerously low reserve of liver function, but also in the treatment of established coma when this has been precipitated by gastro-intestinal haemorrhage. This, of course, only occurs in cirrhotics, as opposed to patients with acute hepatitis, and in this series haemorrhage shortly preceded coma in nineteen instances in the thirty-one cirrhotics.

Haemorrhage

I want to bring out three points in relation to haemorrhage in cirrhosis. Figure 1 shows the interval elapsing between haemorrhage and the onset of coma. As can be seen, we have less than 48 hours in most cases in which to take effective prophylactic action against coma.

The next two figures show the interval in time between the onset of haemorrhage and death. I have had to separate Figure 2, which comprises cases who have survived haemorrhage for many months, from Figure 3, constructed from those who died shortly after haemorrhage, for the sake of clarity. Figure 2 shows that many of these cirrhotics sustained substantial bleeding from oesophageal varices up to a surprisingly short time before death without showing abnormal neurological signs. It shows that gastro-intestinal haemorrhage is not so dangerous if liver function is not too far impaired. But it is possible that repeated or prolonged bleeding progressively reduces hepatic function in these cases and we must not neglect this aspect of the effects of haemorrhage.

It is not uncommon to find a cirrhotic surviving a run of haemorrhages over a year or two, and succumbing to a final bleed which is the first one to be followed by coma. It is worth while recalling that Rappaport, Borowy and Lotto (1952) concluded that hepatic anoxia was the basis of the experimental ischaemic coma they induced in dogs.

Figure 3 shows that once haemorrhage has produced coma, the prognosis is grave. Though haemorrhage and its effects eventually overcame these patients, death occurred more commonly from coma than from exsanguination. In addition to

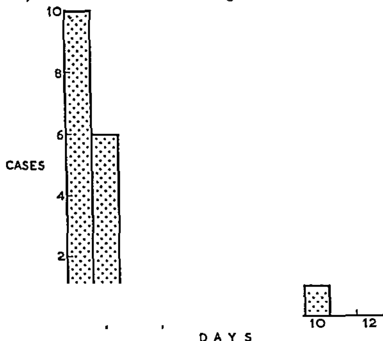


Fig. 1. Interval between occurrence of haemorrhage and onset of coma in nineteen cirrhotics.

transfusion, therefore, it is rational to empty the gut of blood as far as possible after a haemorrhage. Colonic washouts are harmless enough, and purgation may be tolerated even by patients as ill as these, but emptying the stomach entails passing a tube past the bleeding point and this may aggravate the haemorrhage. The Sengstaken tube has been devised to stop bleeding by compression of oesophageal and gastric varices between inflated bags, but it is difficult to handle in semicomatose patients and its advantages when in position may be outweighed by the increase in blood loss attendant on its effective passage. Oral thrombin has been recommended for the

control of oesophageal oozing (Daly, 1947) but, in my experience, has not been helpful.

The capacity of haemorrhage from oesophageal varices to initiate coma and the usual fatality of the coma when it occurs

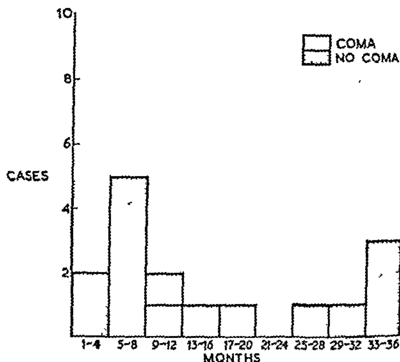


FIG. 2. Interval between haemorrhage and death in sixteen cirrhotics.

underline the importance of prophylactic measures against recurrent bleeding. Shunt operations which involve the opening up of large new portal-systemic channels are not wholly to the advantage of the patient since they increase the dangers of what Sherlock has called *portal-systemic encephalopathy*. The ideal operation for the prevention of bleeding should obliterate established oesophageal varices without opening up new anastomoses. The injection of varicosities by sclerosing fluids as suggested by Crafoord and Frencker (1939) and as carried out by Macbeth (1955) or, better still, direct ligation of submucosal

veins as practised by Phemister and Humphreys (1947), Allison (1950) and Wooller (1955) both come near to satisfying these requirements, and are rational manœuvres even if their temporary effect implies the need for repeated surgical attacks. The

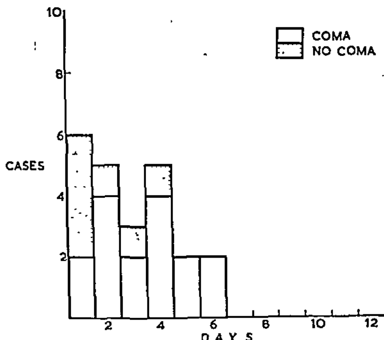


Fig 3. Interval between haemorrhage and death in twenty-three cirrhotics

portal pressure is unaffected or even raised by these procedures, but the theoretical fear of precipitating or increasing ascites does not seem to be justified by events and, as is well known, many other factors are more important in determining the retention of fluid in the peritoneal cavity.

Glutamic Acid

The other way in which the ammonia story bears on the treatment of hepatic coma is in its metabolic relations with glutamic acid. Krebs (1935) in a discussion of the metabolism of amino-acids states that glutamine can be synthesized from ammonia

and glutamic acid fairly fast in the presence of plenty of carbohydrate by animal brain slices; Weil-Malherbe (1950) is of the opinion that glutamic acid plays a prominent role in an enzyme system designed for the removal of intracellular ammonia.

Walshe (1951), in discussing the pathogenesis of hepatic coma, suggests that glutamic acid metabolism in the brain may be interfered with, and the ammonia-binding action of glutamic acid impaired. He also supposes that the reaction: glutamic acid $\rightleftharpoons$ alpha-ketoglutaric acid $\rightleftharpoons$ pyruvic acid may be upset, and it may be significant that both these latter substances are known to be found in the blood in excess in hepatic coma (Watson, 1950; Neefe, 1950; Amatuzio and Nesbitt, 1950; and Butt, 1954). The precise meaning of these changes is not clear, but it would appear that the citric acid cycle is upset in some way (Bessman, Fazekos and Bessman, 1954) and Walshe's suggestion that glutamic acid might at least improve the ammonia-binding mechanism in the brain seems a reasonable one.

There is general agreement, however, that the results of treatment of coma in acute hepatitis with this substance are disappointing. Walshe himself (1955) now subscribes to this view. Three patients in hepatic coma resulting from acute hepatitis in this series received glutamic acid and derived no benefit from it.

Its effect in cirrhotics can only be properly assessed in those cases who have gone into coma without a preceding haemorrhage or in whose cases no active steps have been taken to remove blood from the gut, which in itself might be enough to lighten coma. These criteria are only satisfied by thirteen cases in this series. In these there was definite improvement in eight, no effect in three and doubtful benefit in two. Seven out of the eight who improved subsequently died within a week or two, and glutamic acid failed to control their final coma; the survivor is still enjoying a normal level of consciousness one year after recovery. These figures suggest that there is a case to be made out for giving glutamic acid to comatose cirrhotics, even though the benefit it may confer is only likely to be temporary and it is evidently not the answer to the whole metabolic disturbance present.

Foetor Hepatis

When we look around for consistent metabolic features of hepatic coma other than raised blood ammonia levels, we cannot fail to be struck by hepatic foetor. Recently Challenger and Walshe (1955a) have isolated methyl mercaptan from the urine of a patient with marked oral and urinary foetor, and they believe that foetor hepatis is caused by elimination from the body of this substance, dimethyl sulphide or dimethyl disulphide, both of which might be formed in the body from methyl mercaptan. The pharmacology of methyl mercaptan, CH_3SH, is little known, but Challenger and Walshe (1955b) suggest that it may be toxic by virtue of its close structural relationship to hydrogen sulphide, HSH, and to methyl alcohol, CH_3OH. They postulate methionine as a possible source of mercaptan and note the accumulation of methionine in the blood in hepatic coma due to failure of *transmethylation functions of the liver*. But mercaptans are known to be present in the gut, and it seems possible that they might accumulate in the same way as ammonia. I mention this because I have at times wondered whether foetor is more often present in the coma of acute hepatitis as opposed to that of cirrhosis and that it might indicate the presence of a product of autolysis of liver cells rather than an accumulation of a breakdown product from the gut. In trying to decide this point in retrospect I do not find my Burmese records particularly helpful; in the Orient one's olfactory apparatus is mercifully subject to the physiological principle of fatigue, and I can draw no conclusions. The facts that foetor is not present in cases of cirrhosis in normal consciousness, even in the face of a big collateral circulation, and the persistence of foetor in patients who have received nothing by mouth for as long as ten days argue that it might be associated with hepatocellular autolysis But in this series foetor was noted in roughly equal proportions in the two groups, four out of eight in acute hepatitis, and thirteen out of thirty-one in cirrhotics. It is striking that clinically identical states of coma may be found in association with livers whose histology varies between the widespread destruction and lack of recognizable liver tissue so characteristic of acute fulminant hepatitis and the regeneration

nodules of the cirrhotic, in which the liver cells are surprisingly well preserved. It does not seem reasonable to blame products of their autolysis for foetor or for coma.

Experiments on mice at the Toxicology Research Unit carried out by Dr. Barnes (Walshe, personal communication) suggest that methyl mercaptan might be concerned in the production of unconsciousness in man in the concentrations reasonably anticipated in hepatic coma, but that dimethyl sulphide and dimethyl disulphide can be exculpated in this context. The importance of sulphur metabolism in the production of coma is not yet clear, but its consideration has not so far resulted in any therapeutic advance.

TABLE 3. Composition of faeces

Water
Endogenous fat
Mucus
Epithelial cells
Digestive enzymes
Bile steroids
Inorganic salts of Ca, Mg, Fe, Cu
Micro-organisms
Acetic, lactic, butyric and other organic acids from CHO fermentation
Tyramine, histamine, cadaverine and putrescine by bacterial decarboxylation of amino-acids
Indole and skatole by partial degradation of tryptophane
H_2S, CO_2, CH_4, H_2, NH_3, phenols and mercaptans, all by bacterial action

In my view, the answer to hepatic coma lies in the gut. We have to remember that stools of a sort are passed even by starving patients and Table 3 will remind you of their composition.

Somewhere in this list, it seems, we should find something significant. Cooke (1955) for instance finds that certain indoles are present in increased quantities in the stools of patients suffering from idiopathic steatorrhoea; in two cases he noticed neurological signs similar to those found in hepatic coma; and in one of these cases no liver damage was demonstrated.

It will be observed that bacteria are at work in the production of many of these substances. Members of the tetracycline group of antibiotics have been recommended in the treatment of

hepatic coma in the hope of suppressing or altering some of the metabolic processes carried out in the intestine. These drugs have not been given consistently in this series and I cannot comment on their usefulness. We should remember that the tetracyclines can produce troublesome diarrhoea and this may aggravate the low serum potassium which is not infrequently present in hepatic coma.

Mention must be made here of the views of Gould (1954, 1955) who claims that high dosage intravenous medication with mixed vitamins might be expected to influence hepatic coma, as well as many other states of impaired consciousness, by improving the intracellular metabolism in the brain. Though I believe that this treatment is of benefit to confused alcoholics, I have no experience of it in hepatic coma.

Glucose

Brain cells require not only oxygen but glucose, and it seems reasonable to give large quantities of glucose to patients in hepatic coma, not only to help to form the glycogen necessary for the proper reconstruction of liver tissue (Jones, 1936, Foulk, Butt, Stauffer, Baggenstoss and Gross, 1955) but also to help brain cells carry out their normal metabolic processes including the binding of ammonia.

At the same time glucose will reduce endogenous protein breakdown which in itself may throw further work on the liver. Schoenheimer (1942) has studied the fate of amino-acids in the liver with the aid of heavy nitrogen and deuterium and has shown that they may follow at least four separate lines of intrahepatic metabolism, all of which involve energy. Any manœuvre which reduces the amino-acid level in the blood is justified by this argument alone, apart from any possible toxic effects of raised blood amino-acids on the brain It has been suggested too (Rappaport, 1951) that the infusion of a hypertonic solution might be helpful in reducing the cerebral oedema sometimes found in hepatic coma. There is no evidence that hypoglycaemia is *responsible for any fraction of naturally* occurring coma, though it may be relevant to some aspects of experimentally produced coma in animals. Indeed, the full

picture of hepatic coma may be seen in haemochromatosis or cirrhotics with incidental diabetes with blood sugar levels as high as 300 mgm. per cent, as occurred on three occasions in this series. Nevertheless, glucose remains the one food which can be given to these patients with impunity and is the cornerstone of treatment. Bollman's (1949) observation that dogs given enough intravenous glucose to keep the blood sugar level between 200 and 300 mgm. per cent for 36 hours produced definite bilirubinaemia and marked dye retention in the liver seems to have no counterpart in human medicine.

Since glucose may have to be given parenterally for many days, it is wise to give a concentrated 20 per cent solution so as to avoid iatrogenic electrolyte disturbances, of which the most probable is overdosage with water. Sodium deficiency is not likely to occur in diffuse liver disease in the absence of ascites, but the presence of hypokalaemia has been stressed by Artman and Wise (1953). This demands the close watch on urinary output and state of serum electrolytes that is accorded to any patient unable to take food orally. It may be necessary to give potassium supplements. There is a certain danger in giving potassium into an intravenous drip if the fluid is being delivered into a vein close to the heart

If we give 20 per cent glucose solution into a superficial vein the chances of its thrombosing are high; clots are likely to form even in the face of such factors as hypoprothrombinaemia and thrombocytopaenia which may be present, in this sense to advantage, in liver failure.

So far, we have got round this difficulty by passing a polythene tube and delivering glucose into a large vein, either the inferior vena cava or one of the innominate veins. This technique needs a certain amount of practice and the tube has become occluded by clot sometimes even when in the correct position Furthermore, it carries the risk of inducing hyperkalaemia if potassium supplements are being given, unless extremely close watch is kept on the rate of infusion.

Patients on systemic cortisone treatment for any reason are thought to have a low incidence of phlebitis after intravenous infusions. This is presumably due to the capacity of cortisone

to suppress inflammatory reaction. This has led us to a trial of hydrocortisone added to the infused fluid given by ordinary needle into a superficial vein, in an attempt to circumvent the difficulties of infusion by polythene tube to which I have just referred. We have used 10 mgm. hydrocortisone per litre of 20 per cent glucose. The early results have been encouraging in that our last three cases of hepatic coma treated in this way have failed to show any macroscopic or microscopic evidence of venous thrombosis or inflammation when autopsy studies, as usual, became available. Dr. Polak, whose idea this was, is publishing details of these cases as a preliminary communication and a larger-scale trial of the method is under way.

Further Lines of Investigation

Before I finish, I would like to take a look at the possible angles from which further knowledge of hepatic coma may be gained, as this is an essential prelude to any advance in treatment.

If we consider first what type of case to study, it is necessary to clarify what we mean by hepatic coma. It is important to exclude cases who may be in coma as a result of gross electrolyte disturbance or the effect of alcohol either direct or through conditioned vitamin deficiency. These factors are likely to operate in cirrhotics, and must be carefully assessed In practice we have to study cirrhotics, since cirrhosis is so much commoner than fulminant viral hepatitis.

It is interesting to speculate, for instance, how far alcohol may have influenced the histological findings in the brains of the patients examined by Adams and Foley (1953). Nearly all the cases they studied were cirrhotics, cirrhotics in America are nearly all alcoholic, and the proportion of ethyl alcohol consumed is probably lower than in this country. This gives us a better chance of getting the answer here, where we have a higher proportion of post-hepatitic cirrhosis or cirrhosis of obscure aetiology than in the United States, and our alcoholic cirrhosis is more purely ethylic.

It seems, too, that we might advance by studying those cases of steatorrhoea in which some of the neurological accompaniments of hepatic coma have been observed. It is possible that

investigation of substances such as indoles, which are known to be present in the gut, and which may be found in excess in the urine of patients with steatorrhoea (Aterman, Boscott and Cooke, 1953), may provide a clue as to what fractions of protein breakdown other than ammonia play a part in the production of coma.

Cooke (1955) also calls attention to the frequency of tremor and confusion in the anoxia of cor pulmonale. These cases do not show the pyramidal signs which occur so commonly in hepatic coma (Stokes, Owen and Holmes, 1945) and I do not think they help us much in this context, but they do raise the question as to whether the tremor seen in liver failure is as typical as has been made out. I have serious doubts on this point and I think it is a pity that the term 'flap', previously evocative of nothing more significant than the activities of the third of W. S. Gilbert's three kings of Chikeraboo, should now have acquired a specific hepatic connotation. The tremor may indicate no more than the effects of anoxia in brain cells.

Coma must ultimately depend on interference with neurones, but I doubt whether deeper neuro-histological studies will result in any dramatic advance in therapy. It is only recently that any remarkable changes have been found. In 1952 Adams and Foley, using special methods not easily adapted to routine histological practice, showed swollen and proliferated astrocytes, chiefly centred on the basal ganglia, and occurring most strikingly in the coma of cirrhosis as opposed to the coma of acute hepatitis. Astrocytes are feeding cells, and this suggests that a breakdown of some enzyme system may prevent neurones from accepting food from them, so that they swell. Whatever toxic metabolites produce coma they are, of course, more likely to be accumulated in the blood over a long period of time in cirrhotic cases, and these histological changes may be no more than a reflection of the progressive inability of neurones to accept from their donor astrocytes something necessary for their internal metabolism.

Whatever you may think of the ethics of direct intraventricular injection of substances in man, there is no doubt that Feldberg and Sherwood (1954a, b) have produced some

interesting results with the technique they have devised, and they recognize distinct behaviour patterns in animals in response to the intraventricular injection of individual drugs. They find a [illegible] tachypnoea [illegible] e to stupor, adrenaline results in a state resembling light sodium pentobarbitone anaesthesia, decamethonium produces twitching and spasticity, while banthine results in motor incoordination. This line of attack opens up a new avenue for the investigation of metabolic disturbances affecting brain tissue such as we are discussing today.

It may be that a combination of careful screening of intestinal contents and direct application of component substances to brain tissue through a cannula tied into a lateral ventricle will in time tell us why patients die as a result of severe diffuse liver disease and so allow of a more rational plan of treatment.

In the meanwhile we should not stray too far along the road to therapeutic nihilism. An awareness of the nature of the dangers of haemorrhage and a willingness to use a harmless substance such as glutamic acid may prolong the life of the cirrhotic, provided that the iatrogenic hazards of morphine poisoning and electrolyte imbalance are avoided. And sufficient glucose, given in concentrated form either by polythene tube or in combination with hydrocortisone into a superficial vein, may serve to keep the sufferer from acute hepatitis afloat until nature throws one of her rare and unpredictable lifebelts to the liver cells.

ACKNOWLEDGEMENTS

I wish to thank my colleagues at University College Hospital who have allowed me access to the records of those cases who were not under my care.

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with the mucosal valve as the best candidate, but it still lacks visual confirmation.

Activity of the Lower Oesophagus

Before discussing further the nature of the barrier that prevents the oesophageal transmission of gastric pressure, or the reflux of gastric contents, I shall give an account of the activity of the oesophagus with particular reference to its lower end.

The region is rather inaccessible, and for the most part we must infer its behaviour from observation of swallowed radio-opaque substances, and from records of pressure changes within the lumen. Such records are easily made through small water-filled polythene tubes attached to suitable manometers (Plate XXVII, Figure 1).[1]

When a subject is not eating or drinking, swallowing movements occur every few minutes, but for most of the time the pharynx and oesophagus are quiescent. The oesophagus is then empty and collapsed, being sealed off from the atmospheric pressure by the cricopharyngeal sphincter, and from the intragastric pressure by the cardiac barrier, whose nature need not at once concern us. The intra-oesophageal pressure is therefore virtually the same as the intrapleural pressure, and undergoes similar fluctuation during respiration. Since during inspiration the intra-abdominal pressure rises while the intrathoracic falls, the respiratory fluctuations are useful in showing on which side of the pressure barrier a recording site lies, and whether the barrier is working properly. It is obviously necessary to allow for the respiratory effects before attributing pressure changes to oesophageal activity, and to this end it is usually desirable to record respiratory movements simultaneously.

Let us suppose a subject drinks some barium cream while we observe its passage radioscopically and record the pressure changes at various sites (Figure 2). The subject drinks in a series of gulps, and with each we can record the relaxation of the cricopharyngeal [illegible]
oeso [illegible]
ever [illegible]

[1] The plates referred to in this lecture will be found between pp 400–1.

XXII

The Physiology of the Lower Oesophagus and Cardia

A. C. DORNHORST

THE main fact about the lower oesophagus and its junction with the stomach is this: as one drinks, fluid falls unhindered into the stomach; but if one then stands on one's head, it remains trapped and does not re-enter the oesophagus. There is obviously some special mechanism at the oesophageal-gastric junction.

The surprisingly diverse views of the nature of this mechanism involve one of the following assumptions: (1) an extrinsic sphincter formed by the muscle of the diaphragmatic hiatus; (2) an intrinsic sphincter formed by specialization of the lower oesophageal muscle; (3) a valve formed by the angle between oesophagus and stomach, maintained by support from the liver or by contraction of the well-developed 'sling' muscle which runs along the lesser curve and loops round the oesophageal-gastric junction; (4) a valve formed of mucosa and submucosa only, and maintained by the muscularis mucosae.

In my opinion the evidence is against occlusion of the oesophagus by the diaphragmatic hiatus in normal circumstances. There certainly is specialization of the lowest part of the oesophageal muscle, which I shall describe in detail later, but the prevention of gastric reflux is apparently independent of this. The whole concept of a valve formed by an acute angle of oesophageal entry is a mistake arising from thinking of a three-dimensional problem in two dimensions only. We are thus left

(a)



(b)

FIG 1. Tubes used for simultaneous recording of intra-oesophageal pressure at several sites Each tube is 1 mm in external diameter The closer view (b) shows the lateral hole forming the lowest of the recording sites The distal ends of the tubes are filled with mercury.

as the fluid passes down. At the last gulp of the series the crico-pharyngeal sphincter contracts with more than normal vigour for a few seconds, and this contraction spreads to the top of the oesophagus to initiate a propulsive wave.

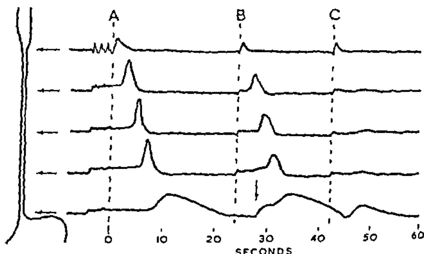


FIG. 2. Composite diagram of pressure changes as recorded at different levels in the oesophagus. Respiratory fluctuations have been omitted. A Propulsive wave initiated by the last of a series of gulps. B. Propulsive wave combined with synchronous contraction of lower oesophagus (marked by arrow). C. Failure of propulsive wave: synchronous contraction preceded by relaxation.

The point to note here is that the propulsive wave is not initiated until the end of a series of gulps—say six, lasting about ten seconds and involving perhaps 300 ml. of fluid. Most of the fluid passes by gravity straight into the stomach with no delay, and the propulsive wave has little to do (Plate XXVIII, Figure 3). Of course this is not so when a solid bolus is swallowed.

We may now trace the propulsive wave down the oesophagus. It travels at a steady rate of about 4 cm./sec. restoring, as it passes, the original negative pressure (Plate XXIX, Figure 4). There is little change in shape or amplitude until the last 2–3 cm. are reached: here the pressure developed is usually less but lasts much longer, taking perhaps 30 sec. to disappear; and in fact the resting state is not regained for about one minute (Plate XXX, Figure 5). That this is so is seen when a further

PLATE XXIX

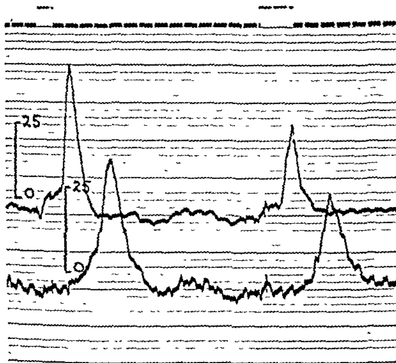


FIG. 4 Propulsive waves passing down central oesophagus. The recording sites are 10 cm apart. In this and subsequent records, time is marked in seconds and the pressure scale is in mm Hg

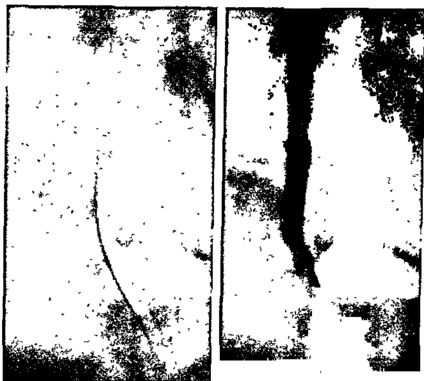


FIG 3 Swallowing through a relaxed oesophagus. The mercury-filled ends of recording tubes can be seen Only 0 5 second separates the two pictures. there is no hold up of barium Compare Fig 7 (Reproduced by courtesy of *The Lancet*)

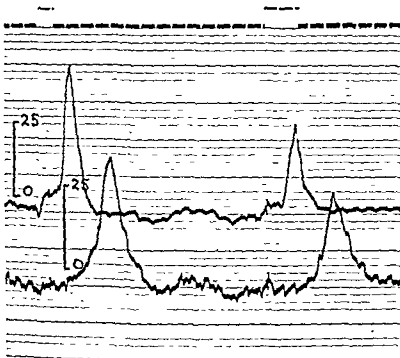


Fig. 4. Propulsive waves passing down central oesophagus The recording sites are 10 cm. apart. In this and subsequent records, time is marked in seconds and the pressure scale is in mm. Hg.

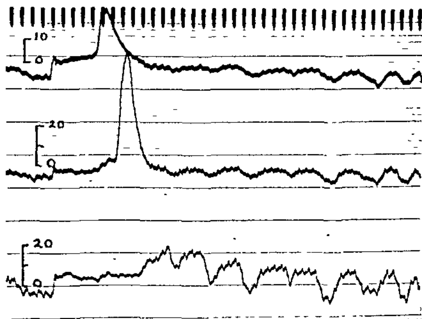


FIG. 5. Pressure approximately 16 and 24 cm. below pharynx and at extreme lower end of oesophagus. The prolonged, low pressure rise and the exaggerated respiratory variation are typical of the latter region. The rise in pressure here at the movement of swallowing indicates the region was *initially relaxed*.

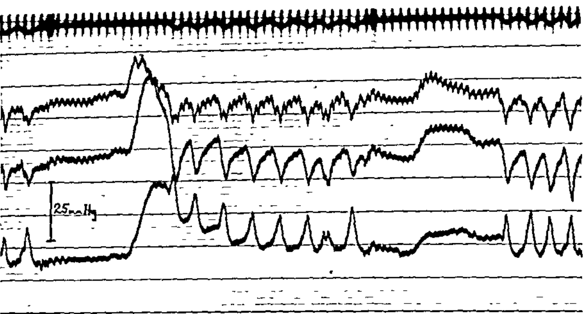


FIG 6 *The upper trace, overlying the time marker, records respiration (inspiration downwards). The next two traces record pressure at sites 9 mm. apart in the lowest part of the oesophagus. The lowest trace is from a site a further 6 mm down, and on the gastric side of the pressure barrier as shown by the inspiratory rises of pressure. The breath has been held for several seconds after each swallow. The first swallow leads to a propulsive wave arriving at the cardiac region in 8–9 seconds. The second swallow provokes only a synchronous contraction at 4 seconds preceded by probable relaxation.*

Plate XXX

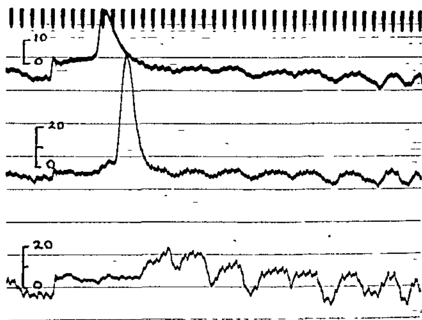


Fig 5 Pressure approximately 16 and 24 cm. below pharynx and at extreme lower end of oesophagus The prolonged, low pressure rise and the exaggerated respiratory variation are typical of the latter region The rise in pressure here at the movement of swallowing indicates the region was initially relaxed.

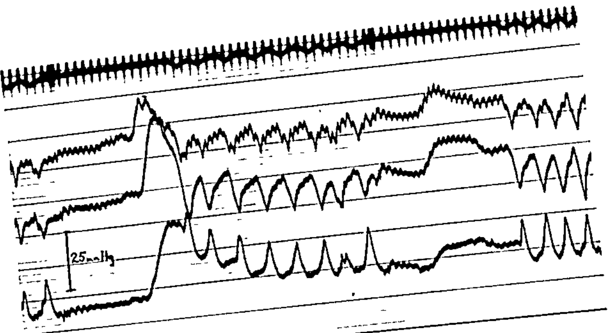


FIG 6 The upper trace, overlying the time marker, records respiration (inspiration downwards). The next two traces record pressure at sites 9 mm apart in the lowest part of the oesophagus The lowest trace is from a site a further 6 mm down, and on the gastric side of the pressure barrier as shown by the inspiratory rises of pressure The breath has been held for several seconds after each swallow. The first swallow leads to a propulsive wave arriving at the cardiac region in 8–9 seconds The second swallow provokes only a synchronous contraction at 4 seconds preceded by probable relaxation.

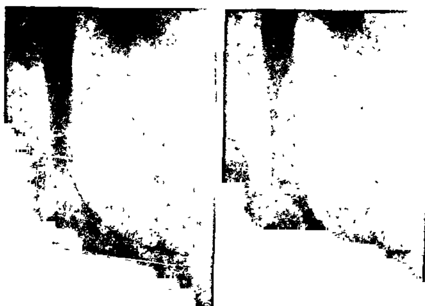


FIG. 7 Swallowing about 7 seconds after a propulsive wave has reached the lower end of the oesophagus; there is a definite hold up of barium which lasted about 2 seconds. Compare Fig. 3.

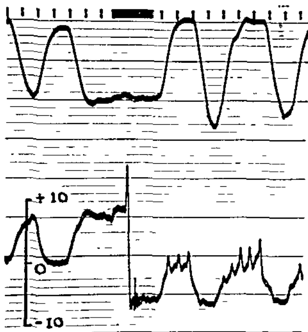


FIG 8 *Upper trace, respiration with inspiration downwards* Lower trace, pressure recorded through an open-ended tube The end of the tube is at first on the gastric side of the pressure barrier At the signal the tube is withdrawn about 1 cm and enters the oesophagus

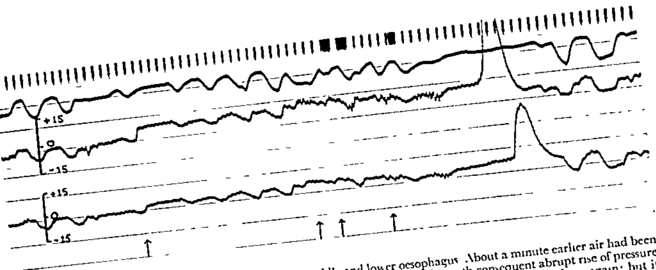


FIG 9 Upper trace respiration Pressures recorded from middle and lower oesophagus About a minute earlier air had been injected into the stomach The first arrow indicates the opening of the cardiac valve with consequent abrupt rise of pressure as the oesophagus fills with air The falls in pressure with the next few inspirations show that the valve closes again; but it opens as indicated by further arrows, and the signals indicate eructation of gas A propulsive wave, by forcing gas back into the stomach, finally restores the original low pressure.

PLATE XXXIV

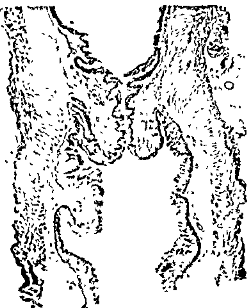


FIG. 10. Section through cardia oesophagus above (Reproduced by courtesy of *The Lancet*.)

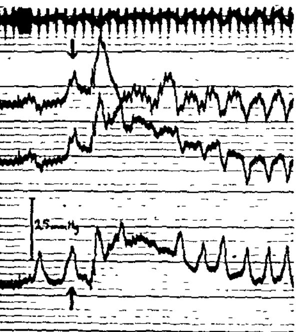


FIG. 11. As for Fig 6. Note, at arrow, the inversion of the respiratory pressure change on the oesophageal side of the barrier.

swallow is made within this period. The propulsive wave though probably somewhat smaller proceeds as before, but in the lower few cm. differences are found. First, there is no immediate rise of pressure at the moment of swallowing, then about four seconds later, that is four to five seconds before the arrival of the propulsive wave, there is a synchronous rise in pressure over the lower 5 cm. or so, which continues up to and merges into the propulsive wave. This rise may be preceded by a short drop in pressure. If a swallow follows another at a still shorter interval there may be no propulsive wave, but the synchronous contraction of the lower end may still occur (Plate XXXI, Figure 6). When fluid is drunk before the resting state is regained, a column of several cm. is definitely held up for a second or two before it can enter the stomach (Plate XXXII, Figure 7).

The conclusion is therefore that when a minute or more has elapsed since the last propulsive wave, the lower oesophagus is inert, but at shorter intervals some contraction lingers even after the local pressure rise has ceased. Moreover in this state, swallowing induces further synchronous contraction, independent of the propulsive wave and at least sometimes preceded by relaxation. This effect might be nervously mediated, or might be caused by the stretch associated with the pharyngeal elevation of swallowing.

The dependence of oesophageal behaviour on frequency of swallowing is responsible, I think, for some apparent discrepancies in the accounts of different authors, and one may add that repeated swallowing of sips of water eventually lead to small and irregular responses A few minutes' rest or the swallowing of something solid restores the original pattern.

The Pressure Barrier

I now turn to the behaviour and nature of the cardiac pressure barrier.

The following experiment, which has been performed several times by my surgical colleague Mr. Kent Harrison, shows that whatever may be the effect of structures extrinsic to the stomach and oesophagus, there is certainly an effective intrinsic mechanism. During laparotomy the stomach is filled with water through

an oesophageal tube which is then withdrawn. With the pylorus clamped, the distended stomach may now be firmly squeezed between the hands without emptying into the oesophagus. Moreover this remains true even when the cardia and lower oesophagus have been completely mobilized as required in some operations; in which case there is no support from neighbouring structures, and the oesophagus makes approximately a right angle with the gastric fundus. It is clear that extrinsic factors are not necessary for cardiac competence. This is not to assert that the maintenance of normal anatomical relations is not helpful, and there is in fact no doubt that when they are disturbed, for example in hiatus hernia, cardiac incompetence is frequent though not invariable.

Pressure measurements show that the barrier separating gastric and oesophageal pressures is remarkably narrow: a pair of recording sites 5 mm. apart span it comfortably. Tubes may be slid through it easily in the forward direction, even during inspiration where a considerable pressure step is present. On withdrawal from the stomach one often records a small spike of pressure followed by a very sharp drop (Plate XXXII, Figure 8). In the immediate vicinity of the pressure barrier and on either side of it the respiratory pressure swings are exaggerated, presumably because the recording site moves in and out of the actual barrier region. An unexpected finding is that the contraction of the lower oesophageal muscle may be recorded on the gastric side of the barrier for a distance of about 1 cm. (Plate XXXI, Figure 6).

The valvular nature of the barrier is striking. It is impossible to maintain a pressure in the oesophagus above that in the stomach, but gastric contents cannot be forced back by the considerable inverse pressures that may be applied. By contrast the valve may open spontaneously from time to time. This may be provoked by injecting air into the stomach, by fizzy drinks or by the classical carminatives such as dill water. The opening of the valve is signalled on the record by a sudden rise of oesophageal pressure to approximately the gastric level and the appearance of inspiratory rises of pressure—that is the pressure within the oesophagus now follows that in the stomach (Plate

XXXIII, Figure 9). Such cardiac opening occurs quite suddenly for a few breaths and then intermits. Since the entry of gastric contents into the oesophagus commonly provokes a propulsive wave which traps it and forces it back, cardiac opening often does not lead to eructation.

The Valve

At this stage I had better say what sort of structure I think the valve has. Plate XXXIV, Figure 10, an operative specimen, may be a lucky fluke but it illustrates what I have in mind. A funnel of mucosa pulled up and maintained by specialized action of the muscularis mucosae would have the properties described. It can be seen that a very modest pressure exerted by the muscularis [illegible]

traction of the muscularis mucosae, by relaxation of the main stomach muscle pulling out the folded mucosa from below, and perhaps by contraction of the muscularis mucosae of the oesophagus pulling it out from above.

Does the proper functioning of the cardiac valve depend on the specialized behaviour of the lower oesophageal muscle? Apparently not, for not only does the valve remain competent when all muscular activity following swallowing has subsided, but patients with symmetrical progressive scleroderma, in whom the lower oesophageal muscle characteristically atrophies with complete lower oesophageal paralysis, often have normally competent cardias. Moreover during the synchronous lower oesophageal contraction described earlier, the cardia may actually open for a second or two (Plate XXXIV, Figure 11). This may perhaps be evidence of activity in the lower oesophageal muscularia mucosae.

There is still much to be learnt about this region, and rapid progress may be expected by simultaneous use of multiple pressure recording and cineradiography which the introduction of the image intensifier has now made feasible.

XXIII

Renal Control of Acid-base Balance

M. D. MILNE

THE maintenance of an almost constant hydrogen ion concentration in the blood and extracellular fluid is one of the most important physiological homeostatic mechanisms. In health, the pH of the plasma varies from 7·35 to 7·45. Death in acidotic coma usually occurs if the pH falls below 7·0, and, at the other extreme, a value of 8·0 is equally lethal. Information regarding intracellular pH is less accurate, but there is no doubt that the body cells are more acid than the plasma. Quantitatively, voluntary muscle is the most important type of cell, since it accounts for 35 per cent of the total body solid. Gardner, MacLachlan and Berman (1952) found the average pH within the muscle fibre was 6·98, which means that the concentration of intracellular hydrogen ion is about 2·5 times that of the plasma. The concentration gradient of hydrogen ion across the cell membrane is increased in states of potassium deficiency, since loss of potassium is corrected by transfer of both sodium and hydrogen ion into the cell (Cooke, Segar, Cheek, Coville and Darrow, 1952). Values as low as pH 6·4 have been recorded in voluntary muscle from potassium-depleted animals (Gardner *et al.*, 1952).

Any abrupt change in body pH is prevented by extracellular buffer systems, especially bicarbonate and plasma proteins, and by intracellular buffers including tissue proteins, phosphatic esters, and the haemoglobin of the erythrocytes. The actual pH of any buffer system is determined by the Henderson-Hasselbalch equation:

$$pH - pK_a = log\frac{[\text{ionized salt}]}{[\text{free acid}]},$$

where pK_a is a constant numerically equal to the pH at which there is equal concentration of ionized salt and free acid. Graphs of this equation relating to buffer systems of especial importance in renal physiology are shown in Figure 1. The equation relating

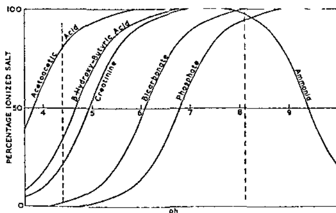


FIG 1. Graph of equation $pH - pK_a = \log \frac{[\text{ionized salt}]}{[\text{free acid}]}$ for various buffer systems of importance in renal physiology. Since ammonia is a weak base, the equation in this case is $pK_a - pH = \log \frac{[\text{ammonium salt}]}{[\text{free ammonia}]}$. The vertical broken lines are the extreme upper and lower ranges of urinary pH.

to plasma bicarbonate and carbonic acid is of great physiological importance. The concentration of carbonic acid in arterial blood is proportional to the partial pressure of carbon dioxide, which is kept constant at 40 mm. of mercury by control of the depth and rate of pulmonary ventilation. Similarly, the plasma bicarbonate is maintained at a level of from 26 to 28 mEq /l. by the renal mechanisms reviewed in this lecture. Any alterations in the partial pressure of carbon dioxide imposed by lung disease, voluntary hyperventilation, or breathing excess carbon dioxide causes a corresponding change in plasma bicarbonate. Similarly, a primary alteration of plasma bicarbonate from renal disease, metabolic abnormalities, or ingestion of acid or alkali will result in a compensatory change of partial pressure of carbon dioxide by appropriate adjustment of ventilation. This tendency to proportionate variation between plasma

bicarbonate and carbon dioxide reduces, but does not completely prevent, potentially harmful pH changes of blood and extracellular fluid.

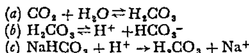
Whilst the chemical buffer systems are invaluable in reducing the rate and extent of reaction changes within the body, they cannot prevent the effects of cumulative additions of acid or alkali. In the general processes of metabolism about 20 mols. of acid in the form of carbon dioxide is formed each day by oxidation of carbohydrates, fats and proteins. This is eliminated by the lungs in the expired air. In addition, from 50 to 100 mEq. of non-volatile acid is produced daily as phosphate from phospholipid metabolism, and as sulphate from oxidation of sulphur-containing amino-acids. In starvation, and to a much greater degree in diabetic ketosis, considerable quantities of acetoacetic and β-hydroxybutyric acids are formed from incomplete oxidation of fats. These acidic metabolic products are excreted in the urine.

In this lecture inorganic electrolytes except ammonium and bicarbonate, e.g. sodium, potassium, calcium, magnesium, chloride, sulphate, and phosphate, will be referred to as 'fixed' anions or cations. Ammonium, bicarbonate and organic acids will be termed 'labile' electrolytes since these substances can be produced or destroyed by metabolic processes. Metabolic *acidosis is a state in which there has been accumulation of fixed* anion in excess of cation, and metabolic alkalosis is the reverse condition. The pH of plasma and extracellular fluid is usually decreased in acidosis and increased in alkalosis. In potassium depletion however, despite a total body acidosis from loss of base, [illegible] ing to tra [illegible] of 'hypo [illegible]

BICARBONATE EXCRETION AND REABSORPTION

Since the glomerular filtration rate in the normal adult is about 120 ml. per minute and the plasma bicarbonate is 26 to 28 mEq./l., about 3 3 mEq. of bicarbonate ion is filtered through the glomeruli each minute Usually the urine is acid and contains virtually no bicarbonate, all the filtered bicarbonate having

been reabsorbed by the renal tubular cells. Bicarbonate reabsorption is now considered to be carried out by a process of exchange of hydrogen ion produced from carbonic acid within the tubular cells, for sodium ion within the tubular lumen. The reactions involved are:



(*a*) $CO_2 + H_2O \rightleftharpoons H_2CO_3$
(*b*) $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
(*c*) $NaHCO_3 + H^+ \rightarrow H_2CO_3 + Na^+$

The hydration of carbon dioxide to carbonic acid is a relatively slow process, but is greatly accelerated within the cell by the enzyme, carbonic anhydrase. This enzymatic reaction can be partially inhibited by the drug, acetazolamide. In therapeutic doses of from 3 to 15 mg./Kg. body weight, only about 20 per cent of the filtered bicarbonate appears in the urine (Counihan

that tubular reabsorption of bicarbonate is chiefly, if not entirely, dependent on exchange of hydrogen ion for sodium ion.

The final urinary reaction therefore depends on the balance between the amount of bicarbonate filtered at the glomeruli and the hydrogen ion secreted by the tubule cells An increase of plasma bicarbonate will tend to produce an alkaline urine, whilst increase of secreted hydrogen ion will cause greater bicarbonate reabsorption and an acid urine. When the two factors are antagonistic, the influence of hydrogen ion secretion is usually predominant.

Typical examples of stimuli causing variation in urinary pH are shown in Table 1. Metabolic acidosis is caused by the direct addition of acidic radicles as in diabetic ketosis or after ingestion of ammonium chloride. Plasma bicarbonate is reduced and the urine becomes strongly acid. Conversely, in metabolic alkalosis, e.g. after ingestion of sodium bicarbonate, plasma bicarbonate is increased and the urine becomes alkaline.

In reaction changes of respiratory origin, e.g. after hyperventilation or breathing 5 per cent carbon dioxide, there is a profound alteration in the partial pressure of carbon dioxide in

both alveolar air and arterial blood. This changes the concentration of substrate for production of hydrogen ion by carbonic anhydrase. It has been shown (Brazeau and Gilman, 1953; Relman, Etsten and Schwartz, 1953; Dorman, Sullivan and Pitts, 1954) that bicarbonate reabsorption, and therefore tubular secretion of hydrogen ion, is directly proportional to the

TABLE 1. Effect of various stimuli on the reaction of the urine

	Plasma bicarbonate	Hydrogen ion exchange	Urinary reaction
Sodium bicarbonate	Raised	Normal	Alkaline
Ammonium chloride	Reduced	Normal	Acid
Hyperventilation	Reduced	Reduced	Alkaline
Respiratory acidosis	Raised	Raised	Acid
Potassium chloride	Reduced	Reduced	Alkaline
Potassium depletion	Raised	Raised	Acid
Acetazolamide	Reduced	Reduced	Alkaline
Sodium sulphate (normal subject)	Normal	Slightly raised	Slightly acid
Sodium sulphate (sodium depletion)	Normal	Considerably raised	Strongly acid

partial pressure of carbon dioxide in arterial blood. Therefore, after hyperventilation the urine is alkaline despite a reduction of plasma bicarbonate. Conversely, after inhalation of 5 per cent carbon dioxide or in chronic respiratory failure from emphysema, the urine is acid although the plasma bicarbonate is increased.

Potassium depletion or excess has a profound influence on acid-base balance, and particularly causes change of intracellular reaction. After ingestion of potassium chloride, potassium ion passes into the cells whereas chloride remains in the extracellular compartment. This causes an increase of intracellular pH with an extracellular acidosis. Owing to reduction

of hydrogen ion available for exchange, the urine becomes alkaline despite a fall of plasma bicarbonate. Diminished hydrogen ion secretion may be interpreted either as directly due to increased alkalinity of renal cells, or as secondary to increased exchange of potassium ion. Berliner, Kennedy and Orloff (1951), who favour the latter alternative, consider that potassium and hydrogen ion share a common exchange mechanism and that increased exchange of one ion will inevitably depress that of the other. In potassium depletion, the renal tubule cells are more acid from loss of intracellular cation (Anderson and Mudge, 1955). There is enhanced exchange of hydrogen ion and the urine is acid despite an extracellular alkalosis with increase of plasma bicarbonate (Roberts, Randall, Sanders and Hood, 1955).

Rapid acidification of the urine may be produced by infusions of sodium salts of variously rapidly excreted anions, e.g sodium sulphate, sodium phosphate, and sodium p-aminohippurate. The effect is much more evident in subjects depleted of sodium or in patients with oedema and sodium retention (Schwartz, Jenson and Relman, 1955). Both hydrogen ion and potassium ion are exchanged in excess for sodium ion within the tubular lumen.

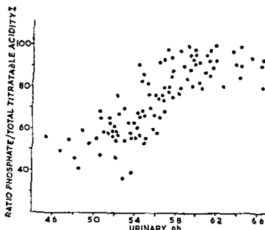
Quantitative Aspects of Hydrogen Ion Excretion

Excretion of hydrogen ion is numerically equal to the sum of urinary titratable acidity and ammonia excretion, less urinary bicarbonate. This amount is equivalent to the excess of fixed anion over fixed cation. Since neither urinary titratable acidity nor ammonia can be excreted in unlimited quantities, elimination of excess hydrogen ion cannot exceed a certain maximal value. If the rate of accumulation of acid is greater than this, e.g. in severe diabetic ketosis, progressive acidosis and death is liable to occur.

Titratable acidity rises with increased excretion of urinary buffers and with reduction of urinary pH. The minimum urinary pH is about 4·4, corresponding to a concentration gradient of hydrogen ion from urine to plasma of one thousand to one. As will be shown later, urinary acidification is impaired in

potassium deficiency, the urinary pH being limited to values above 5·2 or 5·4.

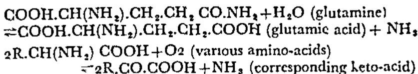
In urine of pH between 5·8 and 7·4, phosphate accounts for almost all of the titratable acidity, but in more acid urine, organic acids, e.g. creatinine, uric acid and citric acid, become



equally important (Figure 2). Except in conditions where urinary buffer is artificially increased, e.g. the infusion of phosphate in acidotic subjects (Pitts, Lotspeich, Schiess and Ayer, 1948), titratable acidity is of less importance than urinary ammonia in the excretion of hydrogen ion and is almost always less than 100 mEq. per day.

Ammonia Synthesis and Excretion

There is little if any free ammonia in arterial blood (Conway, 1950), urinary ammonia being formed within the distal tubule cells by the following reactions:



$COOH.CH(NH_2).CH_2.CH_2\ CO.NH_2 + H_2O$ (glutamine)
$\rightleftharpoons COOH.CH(NH_2).CH_2.CH_2.COOH$ (glutamic acid) $+ NH_3$

$2R.CH(NH_2)\ COOH + O_2$ (various amino-acids)
$\rightleftharpoons 2R.CO.COOH + NH_3$ (corresponding keto-acid)

The former reaction is catalysed by the enzyme glutaminase, and the latter by amino-acid oxidase. In the dog, the hydrolysis of glutamine to glutamic acid accounts for about 60 per cent of urinary ammonia (van Slyke, Phillips, Hamilton, Archibald, Futcher and Hiller, 1943), but it is not certain whether this applies in man.

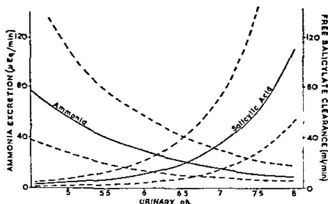


FIG. 3. Variation in ammonia excretion and in free salicylate clearance with respect to urinary pH. Continuous line is the calculated logarithmic regression line in adult subjects; broken lines give the limits at twice the standard deviation. Excretion of ammonia increases in acid urine; excretion of salicylic acid *increases in alkaline urine. Data for ammonia from* Clarke *et al.* (1955); data for salicylic acid from Macpherson *et al* (1955).

Ammonia is one example of a group of weak bases or acids in which excretion is greatly influenced by urinary pH. The bases include ammonia, quinine, nicotine, mepacrine, and procaine, and the acids, salicylic acid and gentisic acids. The excretion of the weak bases is increased in acid urine, the logarithm of excretion being inversely proportional to the urinary pH (Clarke, Evans, MacIntyre and Milne, 1955) Conversely, excretion of the weak acids is greater in alkaline urine (Macpherson, Milne and Evans, 1955). Average adult excretion rates in the cases of ammonia and salicylic acid are given in Figure 3. The excretory mechanism involved is a process of *diffusion across the cell membrane into the urine within the* distal tubular lumen. The membrane is freely permeable to the unionized fraction but is impermeable to the ionized component

(Macpherson *et al.*, 1955). In the case of ammonia, free ammonia is synthesized within the tubule cells and diffuses inwards to the urine and outwards to the peri-tubular fluid and renal capillary blood. In highly acid urine, owing to increased ionization at low pH, more ammonia must diffuse before equilibrium of the unionized component is reached, and therefore excretion automatically increases.

TABLE 2. Factors affecting the rate of ammonia excretion and the concentration of ammonia in the renal venous blood

(a) Factors affecting ammonia transport	Urinary ammonia	Blood ammonia
Increased urinary acidity	Increased	Decreased
Increased urinary alkalinity	Decreased	Increased
Oliguria	Decreased	Increased
Polyuria	*Increased*	*Decreased*
(b) Factors affecting ammonia production	**Urinary ammonia**	**Blood ammonia**
Systemic acidosis	Increased	Increased
Systemic alkalosis	Decreased	Decreased
Potassium depletion	Increased	Increased
Acetazolamide	*Increased*	*Increased*

In metabolic acidosis, ammonia excretion rapidly rises as the urine becomes highly acid With continued acidosis however, excretion rises still further despite a constant low urinary *pH*. This is due to a gradual increase of glutaminase and amino-acid oxidase content of renal tubule cells with consequent rise of ammonia production (Davies and Yudkin, 1952) A similar increase has been shown to occur in potassium depletion (Iacobellis, Muntwyler and Griffin, 1954) and after prolonged ingestion of acetazolamide (Rector, Seldin, Roberts and Copenhaver, 1954). *The common stimulus is an increased acidity of the renal tubule cells* Factors influencing ammonia excretion can therefore be divided into those modifying transport into the

urine, and those modifying rate of production within the cell (Table 2). Greater production by rise of renal glutaminase and amino-acid oxidase will increase diffusion both to the urine and the renal capillary blood. Increased transport into highly acid urine will diminish diffusion outwards to the blood. In contrast to the great physiological importance of urinary ammonia, passage of ammonia into the renal venous blood is usually of no significance since it is rapidly converted to urea by circulation through the liver. It can however occasionally be of importance in hepatic failure, when an increase of blood ammonia may precipitate hepatic coma. The concentration of ammonia in the renal venous blood will be greatest when production is at a maximum, but transport to urine is minimal. This combination occurs during continued ingestion of acetazolamide which causes a systemic acidosis with an alkaline or neutral urine. Many substances containing large amounts of nitrogen are known to precipitate hepatic coma, e.g. proteins, amino-acids, ammonium chloride and urea. Acetazolamide is the only known substance which will cause hepatic coma despite an almost negligible nitrogen content (Webster, 1955).

Although urinary ammonia can increase much more than can urinary titratable acidity, it cannot rise above a certain limiting value imposed by the rate of supply of substrate. If it is assumed that 60 per cent of urinary ammonia is produced from glutamine, it can be calculated that the greatest possible rate of ammonia synthesis would be approximately 650 μEq per minute. This assumes that all plasma glutamine is converted to ammonia in one circulation through the kidney which in fact never occurs. Even in severe prolonged acidosis, the maximum rate of ammonia excretion is rarely greater than 250 μEq per minute, corresponding to an output of about 350 mEq. per day. Since titratable acidity is almost invariably less than 100 mEq. per day, it follows that the maximum limit of elimination of hydrogen ion by the kidneys is about 450 mEq. daily. This corresponds to a daily intake of 24 g of ammonium chloride. A greater intake would inevitably lead to a progressive and eventually fatal acidosis. In renal failure, both the capacity to secrete an acid urine and to synthesize ammonia are greatly

(Macpherson *et al.*, 1955). In the case of ammonia, free ammonia is synthesized within the tubule cells and diffuses inwards to the urine and outwards to the peri-tubular fluid and renal capillary blood. In highly acid urine, owing to increased ionization at low pH, more ammonia must diffuse before equilibrium of the unionized component is reached, and therefore excretion automatically increases.

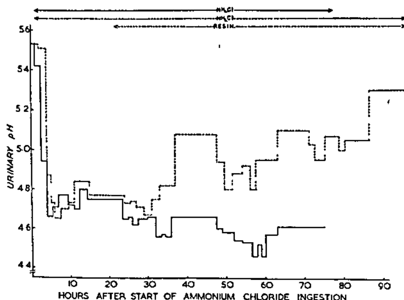
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Acetazolamide	Increased	Increased

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of the kidney to produce a high concentration gradient of hydrogen ion between urine and plasma. In Figure 5, urinary pH during the first three days of ammonium chloride ingestion in a normal subject is compared with that obtained in similar



gent from that of the normal control. Reproduced from paper by Clarke *et al* (1955), by permission of the editor of *Clinical Science*

circumstances during potassium depletion. Urinary pH falls to values below 4 5 in the normal subject, but becomes fixed at between 5·2 and 5 4 in potassium depletion. Total excretion of hydrogen ion is however unimpaired, since, owing to increased cellular acidity, ammonia excretion remains adequate despite an abnormally high urinary pH. Other renal functional defects which have been recorded in potassium depletion (Schwartz and Relman, 1953) include failure of osmotic concentrating power and reduction of glomerular filtration rate, renal blood flow, and Tm_{PAH} (tubular maximal reabsorptive capacity for

impaired. Severe acidosis can therefore be caused by therapeutic doses of ammonium chloride which are quite harmless in the normal subject. In terminal renal failure, the damaged kidneys become unable to compensate for the relatively small amount of fixed acid produced in normal metabolism, and death in uraemic coma then occurs. The limited ability of the kidneys to excrete acid will later be compared with an apparently almost unlimited capacity to excrete alkali.

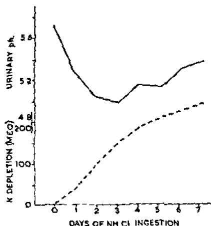


FIG. 4. Effect of continuous ingestion of 8 g. ammonium chloride daily

HYDROGEN ION EXCRETION IN STATES OF POTASSIUM DEPLETION

If ammonium chloride is taken at a constant moderate dosage, e.g. 8 g. daily, the urinary pH falls, and usually reaches a minimum value below pH 4·8 on the second or third day of acidosis (Figure 4). Thereafter, the urinary pH steadily rises until it stabilizes at a pH of between 5·2 and 5·4 despite continued ammonium chloride ingestion and acidosis (Wood, 1955). There is always a negative balance of both sodium and potassium during the first few days of ammonium chloride ingestion, and it was thought possible that the acidification defect could be due to electrolyte depletion. Clarke *et al.* (1955) showed that sodium depletion had no such effect, but in potassium depletion there was progressive impairment in the ability

in mEq. per ml. and V is the urinary volume in ml. per minute.

Since the glomerular filtration rate remains almost constant, the plasma bicarbonate varies directly with the amount of bicarbonate excreted. When equilibrium is reached, the amount of bicarbonate excreted equals the amount ingested. Thus, the plasma bicarbonate concentration produced by a given rate of bicarbonate ingestion can be predicted. Figure 6 shows the relationship between these two variables for glomerular filtration rates of 30, 60 and 120 ml. per minute. It is seen that in normal subjects, very large doses of sodium bicarbonate of over 1,000 mEq. per day are necessary to raise the plasma bicarbonate to values of above 35 mEq./l. Sodium bicarbonate intake of this order, corresponding to about 100 g. per day, is not tolerated by mouth, but can be given dissolved in a milk intragastric drip in the treatment of duodenal ulcer (van

with that expected by theory (Figure 6). In fact, the increase is usually a little less than the expected amount owing to increase of glomerular filtration rate during high sodium intake. These observations show that the normal subject can excrete large amounts of alkali without severe symptoms or any profound disturbance of biochemical homeostasis. The capacity to excrete acid is much more limited, and therefore severe acidosis is more common in clinical medicine than is uncontrolled alkalosis.

In renal failure, with reduction of the glomerular filtration rate, the capacity to excrete alkali becomes progressively impaired and plasma bicarbonate rises much more rapidly after alkali ingestion (Figure 6). In potassium deficiency, owing to increased cellular acidity with enhanced exchange of hydrogen ion, bicarbonate reabsorption is excessive, and therefore the capacity to excrete bicarbonate is impaired Comparatively small doses of sodium bicarbonate, e.g. 200 mEq. per day, will result in much larger increases of plasma bicarbonate to approximately 40 mEq./l. (Evans, MacIntyre, Macpherson and Milne,

PAH). An adequate concentration of potassium is known to be necessary for the efficient action of adenosine triphosphate, the main source of intracellular energy. In potassium depletion the function of the renal tubule cells in maintaining concentration gradients between urine and plasma appears to be particularly impaired. This acidification defect is of greatest practical importance in diabetic ketosis where there is almost invariably an associated potassium depletion. Urine pH is usually fixed at pH 5·4 or above despite severe acidosis and extreme reduction of plasma bicarbonate. An abnormally high urinary pH in diabetic ketosis is probably an important but hitherto neglected sign of existing potassium depletion. Owing to the abnormally high pH, the keto-acids can contribute very little to urinary titratable acidity with consequent impairment of hydrogen ion excretion and intensification of the existent acidosis (Clarke *et al.*, 1955).

Quantitative Aspects of Alkali Excretion

Whilst acid can only be excreted by active secretion of hydrogen ion (Pitts *et al.*, 1948), alkali is excreted by an increase of bicarbonate in the glomerular filtrate. Alkali is therefore excreted with less difficulty than acid, and there is no definite upper limit of excretory capacity as in the elimination of acid. After ingestion of sodium bicarbonate, the plasma bicarbonate and consequently the amount filtered are increased, but hydrogen ion secretion remains unchanged. Normally, the whole of the filtered bicarbonate is reabsorbed by hydrogen ion exchange Therefore:

$$\text{G.F.R.} \times P_{HCO_3} - H^+ = O$$

where G.F.R. is the glomerular filtration rate in ml. per minute, P_{HCO_3} is the plasma bicarbonate in mEq. per ml., and H^+ is the amount of hydrogen ion secreted by the tubules in mEq. per minute.

After bicarbonate ingestion:

$$\text{G.F.R.} \times P_{HCO_3} - H^+ = U_{HCO_3}.V$$

where U_{HCO_3} is the concentration of bicarbonate in the urine

chloride acidosis, in potassium deficiency, and after acetazolamide ingestion, and, conversely, is increased when the cells are alkaline. Organic acid excretion does therefore rise during metabolic alkalosis from bicarbonate ingestion, but in amounts almost invariably less than 20 mEq. daily (Evans *et al.*, 1957). Cooke, Segar, Reed, Etzwiler, Vita, Brusilow and Darrow (1954) have shown that when potassium bicarbonate is administered to potassium-deficient rats, there is a large increase of urinary organic acid without any increase of urinary bicarbonate. A similar effect occurs in man, but on a much smaller scale (Evans *et al.*, 1957). The effect seems to be due to very rapid entry of potassium into cells, presumably associated with an acute rise of intracellular pH. Repletion with rubidium or caesium salts, which pass into depleted cells in place of potassium, is an equally effective stimulus in the rat. In man, this renal mechanism is quantitatively of little or no importance, bicarbonate excretion being the one effective means of elimination of excess base.

In summary, the kidney has been shown to be highly efficient in the maintenance of a constant extracellular pH. The capacity to excrete acid is limited, and progressive acidosis inevitably results from addition of acid at a rate greater than can be eliminated in the urine. There is no definite upper limit to alkali excretion, the healthy kidney being able to excrete alkali at more than three times the rate at which it can excrete acid. In renal failure and in potassium depletion, there is impairment of both acid and alkali excretion with a greater tendency to potentially harmful variation in plasma bicarbonate and plasma pH.

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1957). Total alkali excretion may however remain unimpaired, the amount of bicarbonate excreted being equal to the intake. Large doses of sodium bicarbonate are clearly much more toxic both in renal insufficiency and in potassium depletion.

It is theoretically possible that excess alkali could be eliminated without increase of bicarbonate excretion, the excess fixed

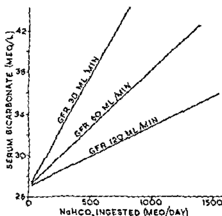


FIG. 6. Graphs of equation G.F.R. $\times$ P_{HCO_3} $-$ H+ $\approx$ $U_{HCO_3}.V$ for

cation being combined with organic acids. This method would be comparable to the elimination of excess fixed anion as ammonium salts during acidosis. It would however be a wasteful process, since organic acids are potential sources of energy. This method of alkali excretion does in fact occur, but usually in negligible amounts. The chief organic acids concerned, in diminishing order of importance, are citric acid, α-ketoglutaric acid, and pyruvic acid (Evans *et al.*, 1957). Citric acid excretion in particular is greatly influenced by variation in acid-base balance. The reaction of the renal tubule cells rather than the pH of the urine appears to be the main determinant of the excretion rate (Clarke *et al*, 1955). Citric acid excretion is diminished when renal cells are unduly acid, e.g. in ammonium

XXIV

Some Anomalies in Endocrine Carcinogenesis

E. S. HORNING

IT is actually inside a generation since the chemist and the biologist have made important discoveries on the causes of cancer, which have been responsible for directing researches into two main channels. There are the extraneous agents such as the carcinogenic hydrocarbons and the ionizing radiations and the inherent agents such as the hormones, then of course there are the genetic factors which influence responsiveness to both these extrinsic and intrinsic agents

I propose to deal with the induction, control and prevention of endocrine neoplasia, and I intend to discuss some of the anomalies which I have personally encountered in endocrine cancer, because very often by studying the exceptions to the general rule we develop a better understanding of such elusive biological mechanisms

I should like to begin by quoting some opening remarks made by Dr. Jacob Furth (1955) of the Cancer Research Foundation, Boston, at the recent Laurentian Conference on Hormone Research and Abnormal Growth. He made the following statement: 'Recent studies have strengthened our concept that there are two basically different types of cancer, one dependent and the other autonomous '

The terms 'hormone-dependent' and 'hormone-independent' cancers were first used by Huggins of Chicago to denote those neoplasms which depend upon hormones for their maintenance and those which grow independently of them. Dependent

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Lacassagne in 1937, Nathanson and Andervont (1939), Cramer and Horning (1938) working independently were among the first to demonstrate that the spontaneous development of mammary cancer in some strains of mice could be prevented, and the incidence of cancer in other strains considerably reduced, by early treatment with a hormone antagonist.

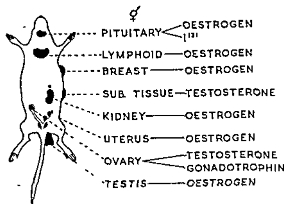


FIG. 1. Endocrine carcinogenesis. Diagram showing site of neoplasm together with responsible hormonal agent

In the clinical field Loeser (1940) was the first to use testosterone in the treatment of breast cancer. In 1944 Haddow and his co-workers, relying on the depression of pituitary function and hence the inhibition of ovarian secretion in preference to employing a hormone antagonist, were the first to use oestrogen for the treatment of breast cancer in women. This treatment was confirmed by Nathanson (1947) who found it to be effective in post-menopausal women suffering from this disease. Pearson (1955) in a recent review claims remission in 45 per cent of cases.

Let us now investigate some of the experimental evidence upon which some of this work we have briefly discussed is based. It is proposed to discuss the induction of tumours of the prostate, kidney, pituitary, testes and ovary (see Figure 1), and also in some instances their prevention by using an appropriate hormone antagonist. These tumours have been purposely selected because in some instances both their induction and behaviour are anomalous.

neoplastic growths, as we know, arise in organs of the endocrine system or else in organs under its direct influence. They are composed of cells which have been stimulated to proliferate because of a hormonal imbalance, and in many instances may be fully or partially controlled by a restoration of the normal equilibrium brought about by a readjustment of the endocrine balance.

Autonomous neoplasms on the other hand, such as those which develop in the skin, stomach, lung, etc., are not under direct endocrine control nor can their growth or behaviour be influenced by any form of hormonal modification. However, as in all biological problems, the dividing line between these two basically different types of cancer is not as rigid as might at first appear, because a certain number of hormone-dependent tumours must obviously give rise to autonomous variants.

When a tumour becomes an autonomous lesion it is composed of permanently altered cells and is freed from its sensitivity to the hormonal forces which control the cells of the endocrine-dependent tumours. It is of course conceivable that some malignant growths might be composed of both the dependent and autonomous cellular components, and this might explain why a hormonal-dependent tumour whose growth has previously been inhibited by means of endocrine therapy, will suddenly lose its responsiveness to a particular hormone, and become an uncontrolled autonomous neoplasm.

In order to appreciate the first endocrinological approach to the cancer problem, we shall have to retrace our steps back to May 1932 when Lacassagne, of the Radium Institute in Paris, published his classical discovery that the naturally occurring oestrogenic steroid hormone 'Oestrone' was implicated in the cause of breast cancer in mice. This was the first demonstration that a hormone circulating in the blood-stream is capable of inducing neoplasia. This experiment of Lacassagne (1932) was in fact the foundation-stone in the pathway of endocrine carcinogenesis Since then, great strides have been made in the induction, inhibition and prevention of certain forms of endocrine cancer in both man and animals by altering their hormonal environment

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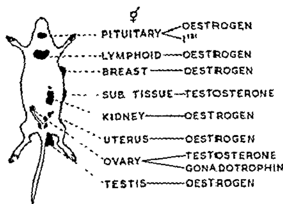


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Carcinoma of the Prostate Gland

There is no doubt that an endocrine dysfunction is an etiological factor in the cause of prostatic cancer in man, for it has been shown that tumours of the prostate can arise by an alteration of the hormonal environment.

In man the growth of most tumours of the prostate can be held in check for considerable periods by the adoption of anti-androgenic measures, as Huggins and Hodges (1941) have admirably shown. The induction, however, of prostatic tumours in rodents and even in many higher animals constitutes an anomaly, for so far there have been no successful attempts to produce malignant prostatic cancer in these animals by the administration of hormonal agents. A glandular carcinoma of the prostate, however, was produced by Horning (1946), not by hormonal administration but by treatment with one of the carcinogenic hydrocarbons, namely 20-methyl-cholanthrene. Slices of mouse prostate, which had been carefully wrapped around crystals of this compound, were implanted subcutaneously into host mice of the same strain. Some of the prostatic tumours which subsequently developed were glandular-cell carcinomas, but most were of the squamous-cell variety. It was found that the glandular cancers could all be successfully grafted into intact mice, but could not all be successfully grown in host mice castrated before puberty. Some of these tumours would grow in castrated mice providing the host animals were treated with testosterone propionate. Later it was found that those tumours which were dependent upon the male sex hormone for their sustained growth as grafts were glandular-cell carcinomas, whereas the prostatic tumours which had become hormone-independent and were growing as autonomous lesions had recently undergone squamous metaplasia during serial transplantation. The glandular-cell tumours were hormone-sensitive, but once they had undergone squamous metaplasia they became androgen independent. These experiments are of interest for two reasons. First, because it was found possible to induce a hormone-dependent tumour in a gland under endocrine control with a carcinogenic hydrocarbon, without the direct intervention of a hormonal agent. Secondly,

because once the chemical constitution of the prostatic cancer cell had altered, it ceased to be dependent on the male sex hormone for its sustained growth. This is in fact, to use the terminology of Furth, an example of an autonomous variant.

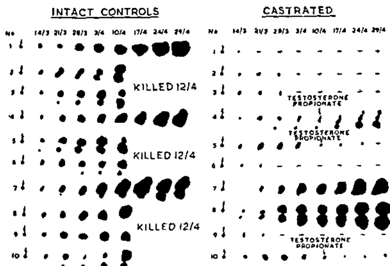


FIG. 2. Silhouette chart showing dependence of transplantable prostatic mouse carcinoma on androgens.

Here is an endocrine-dependent tumour becoming independent of hormonal modification once it had undergone a spontaneous cellular differentiation (see Figure 2). Special emphasis has been laid on this mouse prostate work not merely because it constitutes an anomaly in endocrine carcinogenesis, but also because this work has recently been confirmed and extended by Dr. Mirand (1955) of the Memorial Institute at Buffalo.

RENAL NEOPLASIA INDUCED BY OESTROGENS

Let us now pass on to the induction of kidney tumours by oestrogen administration in the male golden hamster. One of the most interesting findings in the field of endocrine carcinogenesis was made originally by Kirkman and Bacon (1949) of Stanford University. They found that prolonged treatment with naturally occurring or synthetic oestrogens induced kidney

neoplasia in the male but not in the intact female hamster. This work has been confirmed and extended by Horning and Whittick (1954). The several interesting problems which this investigation has brought to light are not yet fully appreciated. For instance, neoplasms in animals other than the hamster which are induced by hormones and are dependent upon them for their sustained growth, generally arise in organs of the body which either belong to the endocrine system or else come under the influence of the anterior pituitary gland. Hamsters are the exception to this rule in that the kidney, except as a part of the body subject to the general stimulation of somatotrophin, is not directly influenced by the pars anterior.

These oestrogen-induced kidney tumours possess all the histological characteristics of malignant lesions. They arise in the cortex in association with either the distal or proximal tubules, and later invade the medulla and the renal pelvis. They also metastasise. Secondaries are seen in the body cavity as well as in the lung and liver.

Another anomaly is that prolonged treatment with oestrogens invariably produces pituitary tumours of the pars intermedia, whereas in other rodents similar treatment induces chromophobe lesions of the anterior lobe.

Absorption Rates of Implanted Pellets

The differences in absorption rate between stilboestrol pellets implanted subcutaneously in the hamster, desert rat and albino rat are illustrated in Figure 3 The absorption rate of the hamster is slower than in the other two rodents, and this might explain why hamsters are able to tolerate such large amounts of stilboestrol.

It will be seen in Figure 3 that a deflection in the absorption rate of the tablets in each of the three rodents occurs on approximately the fourteenth day after subcutaneous implantation, at a period when the pellets become encapsulated. Cowie and Folley (1945) contend that this falling off is due solely to a sudden decrease in the surface area of the pellets.

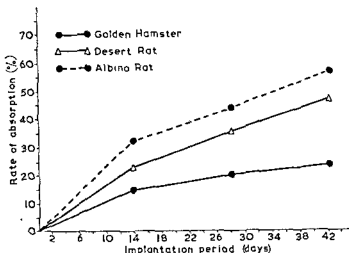


FIG 3 Absorption of stilboestrol in golden hamster, desert rat, and albino rat

HORMONAL FACTORS DETERMINING SUCCESSFUL TRANSPLANTATION

Many unsuccessful attempts have been made to transplant these induced primary kidney tumours into hamsters of both sexes and of varying ages The failure of these kidney tumours to grow either as subcutaneous or intraperitoneal grafts was surprising as they possessed all the histological criteria of malignant lesions.

Consideration was then given to the fact that as the neoplasms are dependent upon high levels of oestrogen for their induction they might also be dependent upon the continued presence of this hormone in excessive amounts for their maintenance as grafts. After a long latent period the grafts grew only in oestrogen pre-treated hosts.

One of the most interesting features is the long latent period which exists between tumour transplantation and the appearance of palpable lesions. A tumour now in its eighth generation of serial transplantation is seen in the following histogram (see Figure 4). It will be noticed that the duration of the latent period between transplantation and the appearance of a palpable lesion shows a marked decline in each successive serial graft.

Even although this kidney tumour has been grafted for several years and the latent period has been reduced from nearly twelve months to four weeks, before palpable lesions develop this tumour still retains its dependency upon oestrogen for

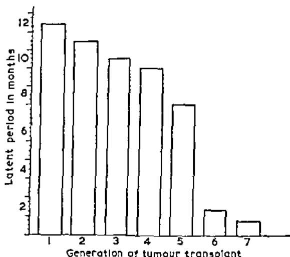


FIG. 4. Histogram showing decline in latent period preceding growth of graft.

maintenance as a graft. If transplanted into untreated hamsters *the tumour will no longer grow*.

These oestrogen-induced grafted kidney tumours conform in their behaviour with many other types of hormone-dependent transplantable tumours observed in laboratory animals. Experiments were therefore undertaken, and are still in progress, to determine whether or not these primary transplantable tumours are capable of growing following abrupt withdrawal of the hormonal stimulus. Removal of the stilboestrol pellet from the subcutaneous tissues is easily achieved, and is followed by a gradual regression of the primary tumours The regression is particularly easy to follow in grafts which have been implanted in the tail of host hamsters The effect of this withdrawal upon the secondary and transplanted lesions is still under consideration. As these kidney tumours are hormone-dependent for their sustained growth, experiments were also undertaken to

determine if tumour formation could be prevented by simultaneous treatment of the host with stilboestrol and its antagonist, testosterone propionate. If renal neoplasia could be prevented by this means, this would be additional evidence of the endocrine nature of tumours arising in a gland which is not under the direct influence of the endocrine system.

Prevention of Stilboestrol-induced Renal Tumours with Testosterone Propionate

The set up of this experiment was simple. Sixty male hamsters all twelve weeks of age were divided into three separate groups, each consisting of twenty animals. The first group were treated with stilboestrol alone, the second received combined treatment with stilboestrol and testosterone propionate, and the third group were untreated.

Examination of Table 1 shows that with the exception of one, all the stilboestrol-treated hamsters developed palpable kidney tumours at various intervals up to ten to eleven months after the commencement of treatment. All these renal lesions were bilateral and multifocal and varied considerably in size. The size of the growth does not always depend upon the duration of treatment. For instance, the single hamster in this group which developed no palpable tumour at the end of this period of treatment, was found at post mortem to possess naked-eye cortical lesions in each kidney. None of the hamsters receiving the combined treatment with stilboestrol and testosterone developed any kidney tumours (see Table 1). The testes and seminal vesicles, in contrast to those treated with stilboestrol alone, showed no atrophic changes. It will also be noticed that no spontaneous kidney tumours appeared in the group of animals which received no treatment (see Table 1).

These experiments with a hormone antagonist demonstrating conclusively that kidney tumours in the hamster can be prevented by combined treatment with stilboestrol and testosterone provide additional evidence that renal neoplasia in the hamster comes under the category of hormonal cancer.

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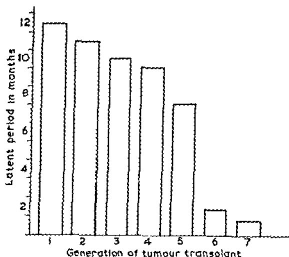


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Ever since Price in 1941 by grafting the ovaries of rats on to the ears of litter mates demonstrated that the difference in temperature stimulated the secretion of androgens instead of oestrogen, it has been shown that under certain conditions a reversal of sex hormone secretion can also occur in the testis. Bielschowsky (1954), in an ingenious experiment on induced cryptorchidism in rats, has demonstrated that the interstitial cell-stimulating hormone of the pituitary leads to a hyperplasia of the Leydig cells of the testis, which are normally associated with the secretion of androgen, but which do under these conditions elaborate oestrogens in sufficient amounts to induce proliferation of the mammary epithelium in the operated hosts. These results of Bielschowsky are of interest when examining the testes of men with breast cancer. There are indications that these breast tumours may have developed as a result of a hormonal imbalance. Frozen sections were cut off the testes after they were imbedded in gelatine. They were then stained with Sudan IV.

The cells of the adrenal cortex, the theca interna off the ovary, and the interstitial cells of the testis all contain lipids in their cytoplasm which are associated with the formation and storage of steroid hormones. A large part of the lipid is in the form of cholesterol which gives a positive reaction to the Lieberman-Burchardt test. Fat soluble dyes like the Sudan series stain the total lipid *and naturally do not distinguish between specific* steroids Cytological examination of these human testes from men with breast cancer showed abnormal increase in the number of the Sertoli cells in the seminiferous tubules and a marked proliferation of the Leydig-cell tissue. Whether or not the abnormal amounts of steroid hormones elaborated by the testes in these instances initiated breast cancer and can be regarded, as Dr. Furth would say, as the intrinsic agent in the etiology of the disease, can only be regarded as a matter of speculation. It does, however, warrant further examination.

Discussion

Let us briefly review some of the anomalies we have encountered in the induction of tumours of the ovary, prostate and kidney

TABLE 1. Prevention of stilboestrol-induced renal tumours in the male golden hamster with testosterone propionate

No. of hamsters	Form of treatment	Duration of treatment	Results
20♂	Stilboestrol alone (20 mg. pellets)	10½ months	18 palpable renal carcinomas 2 early cortical tumours (not palpable)
20♂	Stilboestrol + testosterone propionate (20 mg. stilboestrol) (2.5 mg. weekly in oil)	16 months	No renal tumours developed 1 hamster developed a unilateral hydronephrosis
20♂	No treatment	16 months	No spontaneous kidney tumours

INDUCED OVARIAN TUMOURS

We shall now pass on to another anomaly in endocrine cancer. This deals with the induction of ovarian tumours following regular administration of the male sex hormone commencing 48 hours after birth.

These ovarian tumours were all theca-cell lesions and were induced in albino rats eighteen months after the commencement of treatment. These tumours are of interest for two reasons; first because the ovary itself is a target organ of the endocrine system; and second, because testosterone has never been seriously regarded as a potential carcinogenic agent, although Lacassagne (1939) had claimed that repeated inoculations with the male sex hormone, under strictly controlled conditions, induce subcutaneous sarcoma

HORMONAL IMBALANCE IN MAN

I pass now to the possible association of breast cancer in man with a spontaneous hormonal imbalance. It is established that in women the ovary, although not the sole source of oestrogen in the body, plays an important role in the etiology of mammary cancer. Huggins and Moulder in 1945 were the first to demonstrate that the Sertoli cells in the testis of the dog produced oestrogenic hormones.

organ which is strictly not a member of the endocrine system and moreover does not come under the direct control of the anterior lobe of the pituitary gland. Furthermore, these kidney tumours are hormone-dependent lesions since the tumours regress following abrupt withdrawal of the hormonal stimulus, even although they are capable of metastasising via the lymphatic pathway. The induction of kidney tumours in the hamster is an interesting exception to the general rule, since other species of rodents after similar treatment never develop renal carcinoma. Preliminary experiments still in progress suggest that the liver of the hamster differs from that of the rat, mouse and guinea-pig, in that it is unable to cope adequately with the inactivation of oestrogens. Also other experiments have demonstrated that the renal epithelium of the hamster is endowed with a peculiar susceptibility to renal neoplasia. The results obtained with stilboestrol suggested the possibility that kidney cancer in the hamster might possibly be due partly to absorbed chemical carcinogens acting selectively on the renal epithelium during excretion. This contention was strengthened by the fact that kidney tumours could be induced in the hamster by subcutaneous injection at a remote site with 3:4 benzpyrene, while none developed in albino rats following similar treatment. It was of further interest to record that this particular carcinogenic hydrocarbon has been shown by Cook and Dodds (1933) to possess oestrogenic activity.

Another peculiarity about the hamster is the development of tumours of the pars intermedia, whereas other rodents following oestrogen treatment only develop chromophobic lesions of the anterior lobe of the pituitary. Taking into account this unique response of the hamster pituitary to oestrogen treatment, experiments are being undertaken to determine whether kidney tumours could develop in the absence of a functioning pituitary.

of oestrogen in the hamster is a direct or an indirect effect. This would yield additional information on the mechanism of renal tumourigenesis in these animals.

before discussing the general problems of endocrine carcinogenesis.

The production of ovarian tumours in the albino rat following massive doses of testosterone propionate was first observed by the late Mr. Harold Burrows some years ago at the Chester Beatty Research Institute. Recently I confirmed his contention. The neoplasms were all theca-cell tumours. The histogenesis of these lesions is obscure, but many workers regard them, and I believe quite rightly, as endocrine lesions arising from the stromal cells of the ovarian cortex. The results were surprising not only because the ovary is a target organ of the endocrine system, but also because testosterone has never seriously been regarded as a potential carcinogen. What then is the rationale?

When I discussed these unpublished results at the last Gordon Conference in New London, Dr. Engel (1955) said he was not surprised since he had recently discovered that testosterone was converted in the body into oestradiol. Pearson, working at the Sloan Kettering Institute, New York, contends that androgen sometimes accelerates the growth of mammary cancer in women, which he attributes to the possible conversion of androgen into oestrogen. The reason why progesterone occasionally stimulates instead of inhibits tumour growth in women might likewise be due to the same cause.

In view of these results, the recent work of van Eck and Chang (1955) is of direct interest. They found that ovarian tumours in rodents develop more readily in testosterone-treated X-rayed mice than they do in X-rayed animals which have not been treated with male sex hormone. When considering that after injection androgen might possibly be converted into oestrogen, the known capacity of the gonadal hormones to stimulate mitoses of fibrocytes should also be taken into consideration.

If this conversion does occur in vivo, then it should be possible to induce renal neoplasia in the hamster by prolonged treatment with the male sex hormone alone. These experiments are already in progress.

We have also seen in the case of the hamster that continuous administration of oestrogen can induce kidney carcinoma in an

tumours in mice by treatment with a carcinogenic hydrocarbon alone without the direct application of a hormonal agent, as we have just seen, constitutes an anomaly, some information of interest was brought to light regarding the factors regulating the behaviour of the malignant cancer cell to the male sex hormone. As long as the prostatic tumour cells remains a glandular cell carcinoma it is hormone-dependent, but as soon as it undergoes squamous differentiation it ceases to be dependent upon androgen for its sustained growth and immediately transforms into an autonomous lesion. The question therefore arises: Does the endocrine-dependent cancer cell differ in its chemical composition from the autonomous malignant cell which has lost its responsiveness to the hormone-restraining forces? In other words does this change from dependency to autonomy involve any fundamental change in cellular chemical patterns and metabolism? Unfortunately, these questions cannot be answered since the normal mechanism of hormone action is not yet fully understood. It is thought that hormones constitute an important set of enzyme-regulating factors whose mode of action might be elucidated by the study of hormone-enzyme relationships. Nor as yet is anything known as to how a hormone acts in producing an abnormal cellular state.

Until this problem is more fully appreciated, it will be impossible to comprehend the factors involved in inducing an endocrine-dependent cancer to develop spontaneously into an unrestrained growth or autonomous variant. In the particular mouse prostatic carcinoma which I have mentioned, the cancer cell before it metamorphoses from a hormone-dependent into an autonomous lesion undergoes a pronounced cellular differentiation, and by histological examination it is therefore possible to predict beforehand the response of this tumour transplant to hormonal modification.

Unfortunately this phenomenon is the exception to the rule. Nevertheless it might provide suitable material when one endeavours to elucidate certain aspects of this fundamental problem. The differences in the behaviour of endocrine and non-endocrine-dependent neoplasms are important when thinking in terms of chemotherapy. It is not possible in other types of

One of the most fascinating features of endocrine tumours is their dependence upon a particular hormone, and the dramatic manner in which many regress once the hormonal stimulus is withdrawn. In the case of renal neoplasia in the male hamster we find that changes produced by oestrogen are reversible and last only as long as oestrogen is available to maintain the tumour. Another feature of interest in hormone-dependent transplantable tumours in laboratory animals is the long latent period which exists between implantation and the development of palpable lesions. As we have seen the latent period is gradually reduced during each successive serial generation of transplants. These renal tumours are now in their eighth serial generation, and are still hormone-dependent since they will not as yet grow in non-oestrogenized hosts. This is of exceptional interest, as there is a tendency for most endocrine-dependent neoplasms growing in experimental animals gradually to lose their dependence upon a particular hormone after they have been transplanted for several generations. There are only a few exceptions to this rule. Mühlbock (1954) in Amsterdam induced a rodent ovarian tumour by administration of pituitary gonadotrophins. This particular tumour is now in its fourth year of serial grafts and is still dependent upon either androgens or oestrogens for its maintenance. There are no indications that it will develop into an autonomous variant.

The question naturally arises as to whether the oestrogen acts directly on the tumour cell of the graft or whether the hormone brings about changes in the pituitary gland which in turn indirectly stimulate the latent tumour cell into its malignant phase. The long periods in which these tumour cells remain quiescent as subcutaneous grafts suggests that the pituitary might possibly be involved. In view of this, normal untreated male hamsters are now receiving transplants of pituitary tumours prior to the implantation of kidney carcinoma grafts. If these renal grafts will grow in non-oestrogenized hosts bearing pituitary tumour implants, it would give valuable information on the biological mechanism controlling the behaviour of hormone-dependency.

Although the induction of hormone-dependent prostatic

Data is now accumulating on the effects of hypophysectomy on patients suffering from breast cancer. Some of these reports deal with patients having disseminated carcinoma who have had an adrenalectomy but have suffered a relapse after varying periods of remission. In the last resort a hypophysectomy has been done. In several of these cases a further rapid regression of the carcinoma has been obtained. In others in which reactivation of the growth had occurred, following gonadectomy and adrenalectomy, post-mortem examination has revealed the presence of accessory cortical adrenal rests. These were apparently the cause of the reactivation of the growth. Recurrences of this kind after a remission, in the absence of ovaries and adrenal glands suggests that the anterior pituitary, in attempting to maintain an equilibrium, is capable of stimulating the hypertrophied adrenal rests to secrete oestrogen in sufficient amounts to reactivate the quiescent neoplasm. Pearson contends that there is also evidence suggesting that the reoccurrence of some breast carcinomas is due to a pituitary hormone or hormones acting in addition to oestrogen. Indeed, accessory cortical tissue is not always found in cases which have undergone reactivation. One wonders whether prolactin acting alone or in combination with other pituitary hormones will not eventually be found to play an important role in this complicated story.

Remission of endocrine cancer, whether obtained by a hormone antagonist, or by depression of pituitary function by oestrogens, or by surgical removal of the gonads and adrenals, is only temporary in duration Sir Stanford Cade (1955) in a recent review of one hundred cases states that remission following adrenalectomy and maintenance on cortisone varies from several months to three years. Huggins of Chicago, who initiated this form of surgical therapy, claims remissions, in some instances up to six years

There are many gaps in our knowledge and perhaps more concentrated study of some of the anomalies in endocrine carcinogenesis will help in the final solution of this problem. The fact that some types of endocrine cancer can in many instances be fully or partly controlled by an alteration of the hormonal environment of the host is, to say the least, encouraging.

known tumours either in animals or in man to ascertain by histological methods whether a particular tumour is hormone-dependent or not. Huggins, however, does contend that any breast cancer which has undergone anaplastic changes is invariably more resistant to hormone therapy.

Ever since Huggins and Scott in 1945 first used gonadectomy combined with bilateral adrenalectomy for controlling the growth of breast and prostatic cancer in man, many attempts have been made to find some method by which it would be possible to predict before operation whether the tumour was a hormone-dependent lesion. A promising step has been made recently by Pearson (1955) and his co-workers in New York. They found that measurements of urinary calcium excretion in men with prostatic cancer revealed the existence of two kinds of osteolytic metastases. one dependent on oestrogen and the other non-dependent. It is the former type of patient who responds to adrenalectomy which reduces oestrogen production and thus brings about a remission of tumour growth. Additional investigations may well confirm these findings and establish the value of urinary calcium determinations as a guide to the form of therapy to be taken in prostatic and breast cancer.

Recently Hadfield (1956) has also been studying methods by which it is hoped to determine beforehand whether or not patients with breast cancer possess hormone-dependent tumours. This author is of the opinion that breast tumours are more likely to regress when the production of oestrogen is diminished and the output of gonadotrophin in the urine is increased. He claims to have identified a mammatrophic factor from human urine. This factor has no oestrogenic activity, and it is not apparently found in the urine after hypophysectomy. Hadfield admits that the mammatrophic substance present in human urine is probably prolactin It is known that the prolactin content of urine goes up during parturition and it will be necessary to distinguish between prolactin urinary output occurring normally at various times and ages from that which they claim to be indicative of breast cancer. If these tests can be made truly reliable for the clinical detection of hormone-dependent breast cancer, treatment by hypophysectomy would be established on a firmer basis.

XXV

Recovery from the Lethal Effects of Radiation[1]

J. F. LOUTIT

In the last ten years protection against ionizing radiation has become a matter of very considerable importance. Formerly it was a matter of concern only to those few who were routinely exposed to radiation. The radiation was from X-rays in medical diagnosis and therapy and in industrial radiography; from gamma rays in similar occupations; and in the then limited academic fields of radio-chemistry and nuclear physics. Since the discovery of nuclear fission, however, occupations necessitating exposure to ionizing radiation are increasing daily and will continue to involve more and more people. Permissible daily or weekly doses of the various kinds of radiation have been assessed; but, apart from routine, there is always the prospect of accident in which considerably greater doses may be received.

Routine protection now as heretofore is a matter of prophylaxis. Sources of radiation must be surrounded with shielding material such as lead or concrete which must physically prevent the radiation from reaching the operative. Internal contamination of the body with radioactive materials must be prevented by a most scrupulous attention to detail of laboratory and industrial technique. But in accidents—or for that matter of fact in nuclear warfare—these conditions do not obtain and men may receive serious over-dosage. For the physician this poses the problem, Can the body be conditioned against the effects of

[1] An earlier version of this paper was presented at the Radiation-Biology Symposium, Melbourne, December 1955

Let me conclude as I began by quoting a pertinent remark by Dr. Jacob Furth. 'Recognition and adjustment of the hormonal disturbance in this disease is in fact cancer prophylaxis.'

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a lethal dose of X-rays This hypothesis seemed to be strongly confirmed by work from the National Cancer Institute at Bethesda. Egon Lorenz and his colleagues (Lorenz, Congdon and Uphoff, 1952) showed that not only was normal spleen effective in therapy, but normal bone marrow was equally good. Jacobson had implanted normal spleens intraperitoneally. Bone marrow is not a discrete organ like spleen but a diffuse tissue. Lorenz, therefore, injected suspensions of bone marrow intraperitoneally and later intravenously with even better results. This was a considerable technical gain. Moreover, Lorenz made the notable discovery that therapeutic potency was not confined to normal mouse bone marrow but that normal guinea-pig bone marrow would also serve though larger doses were necessary. This seemed to identify the active principle as a chemical agent. The alternative hypothesis to chemical stimulation of the damaged marrow would be colonization of the affected marrow by normal cells from the injection or the implant and regrowth of marrow from the seeded cells. However, it is an axiom supported with much experimental evidence that transfer and growth of cells from one species of normal animal to another does not occur. It is barred on immunological grounds. Such heterografts even if they do 'take' initially are soon rapidly thrown off as the recipient develops an immune reaction which destroys the graft. Therefore, in this case seeding or colonization seemed to be ruled out and a chemical agent favoured. Furthermore, in San Francisco, Cole and his colleagues at the Naval Radiological Defence Laboratory (Cole, Fishler and Bond, 1953) began to refine the suspensions which they used for injection. In the first place the tissues were subjected to more severe treatment than is required simply to make a suspension. They were ground in a Potter-Elvejhem homogenizer with a special medium and such homogenates were proved active. Separation of the various fractions of the homogenate by ultracentrifugation showed that the mitochondrial and microsomal fractions of the cells were without effect but the nuclear fraction was the potent one.

Our own work at the Radiobiological Research Unit at Harwell (Barnes and Loutit, 1953) began after Jacobson's

over-exposure or if over-exposure has occurred can treatment alter the subsequent chain of biological events?

For the purposes of this discussion we will consider only over-exposure to external radiation and only over-exposure to X or gamma radiation. Also, while considerable investigation has been carried out on prophylactic measures through chemical means no method which yet gives promise of practical application has been uncovered. Therefore, we will consider only recent advances in potential therapy.

Injection of Haemopoietic Tissue

From the viewpoint of experimental medicine the first real progress in this field was made by Leon Jacobson and his colleagues in Chicago (Jacobson, 1952). Jacobson had observed that mice given penetrating X-rays to the whole body died with aplastic anaemia after a certain critical measured dose. Presumably the dose of radiation given to the bone marrow was not greatly different from the dose recorded in air. On the other hand, mice given injections of radioactive strontium which localizes most strongly in the bones, whence the beta rays irradiate the marrow, need a much larger calculated dose of radiation in the bone marrow to cause death from aplastic anaemia. It, therefore, occurred to Jacobson that the spleen of mice, not irradiated to any great extent by radiostrontium, but irradiated along with the rest of the body by X-rays, might be exerting a protective effect in the former case. In support of this thesis was his experiment wherein mice were totally irradiated with X-rays except for the spleen which was shielded by lead. This approximately doubled the dose of X-rays necessary to kill the mouse. Later it was shown that a similar experimental result could be obtained by irradiating the mouse totally but in addition treating the mouse subsequently with an implant of spleen from normal mice. To Jacobson this signified that the normal mouse spleen—either protected from the X-rays given to the rest of the whole body or administered therapeutically after total irradiation—contained a humoral agent which caused accelerated recovery of the damaged bone marrow and allowed the mouse to survive what otherwise would have been

poorer results and below that usually no result The minimal effective dose is about 10^6 nucleated cells. (Others have reported even lower effective doses.) Similar suspensions from spleens of strain-A mice give comparable survival at 30 days However, if the mice are not then killed, for histological purposes or because of shortage of accommodation as is so often the case, but are allowed to live till spontaneous death, a difference between the groups given isologous and homologous material is readily observed. Our unirradiated CBA mice have a median life-span of about 900 days; those irradiated at the age of about 100 days and treated with isologous spleen live for a median period of 500 days longer; whereas those irradiated at 100 days and [illegible] a few months longer [illegible] investigated the cause [illegible] the cellular theory as follows. Normally mice will not tolerate a homograft any more than a heterograft for more than about ten days. By this time they begin to develop an immune reaction against the foreign antigens, and the reaction of antibody with antigen results in death of the cells carrying the antigen. However, the capacity of the mammal to form immune antibodies is impaired after massive doses of radiation. It is possible to conceive that the mouse tolerates a homograft for longer than normal and only recovers its ability to form the appropriate antibody after some weeks or months or even longer; when it does recover this faculty, the graft is belatedly destroyed Transposing the hypothesis to the irradiated CBA mouse, one could postulate that myeloid spleen-cells of strain-A mice colonize and grow in the CBA mouse and form a significant part of the recovered mouse's bone marrow; but, when the reaction of immunity is restored to the CBA mouse, it develops antibodies against A cells which destroy much or all of its effective A marrow. It is also possible to postulate an opposite view. The myeloid A tissue from the donor grows and gradually differentiates, not only into mature red and white blood cells, but also into reticulo-endothelial tissue with the capacity to form antibodies. This donor tissue, therefore, can in theory form antibodies against the host and kill it.

preliminary report and when his humoral theory seemed most likely. However, our attempts to prepare active extracts of spleen from mice and other mammals were fruitless and this is the experience of every other worker who has tried. It was observed that the intraperitoneally implanted spleens appeared to 'take' and survive. We returned, therefore, to first principles to rule out the celullar hypothesis of seeding. We confirmed that suspensions were in practice more effective and more easily administered and that the intravenous route was superior to the intraperitoneal. This was difficult to explain on the humoral theory but in accord with expectation if seeding were taking place.

The agent in spleen or bone marrow is extremely thermolabile. It is destroyed in a few hours at room temperature and is not preserved at 4° C. or -15° C., the usual conditions of storage for unstable biological agents. We (Barnes and Loutit, 1955a) have shown, however, that it is preserved by a technique of storage in glycerol at low temperatures which has become standard for preservation of whole cells.

Originally we could not make our mice of the inbred CBA strain recover with suspensions of spleen or bone marrow from guinea-pigs or rabbits. Heterologous material from foreign species having been ineffective, we turned our attention more to homologous material from different strains of mice. Tissue from mice of the same in-bred strain should be genetically and antigenically identical (isologous); tissue from mice of different strains is genetically and antigenically more or less different (homologous). The CBA mouse was always used as the irradiated subject. 950r X-rays (240 kv., 15 ma., HVL = 1·2 mm. Cu., 43r/min.) has been virtually 100 per cent lethal to these animals untreated. If they are given intravenous injections of suspensions of spleen-cells from infant CBA mice a satisfactory

from four infant spleens (about 100 mg.) in 0·4 ml. of normal rabbit serum are usually tolerated. Suspensions of 1/10th of a spleen give equally good results, 1/20th of a spleen definitely

response within a few days. If the animals were not immune the tumour would grow for about ten days and only then regress. The test-animals were thus killed ten days after a subcutaneous injection of Sarcoma 1 given ten days after their test-injection of tissue or tissue fluid. The results indicated that spleen, lymph glands and induced peritoneal exudates in the irradiated CBA mice treated with A spleen contained A antigen for at least seven weeks. Normal unirradiated CBA mice injected intravenously with suspensions of A spleen contained A antigen for at the most one week only. In a second set of experiments CBA mice given sublethal doses of 500r were given suspensions of spleen from A mice immunized against *B. typhosus H* antigen. The irradiated mice were found to develop agglutinating antibodies against *B. typhosus* which increased with time, indicating the survival and function of the donated material.

We believe that, though all the foregoing results could be accounted for by the transference of a chemical antigen from the donor and its adoption by the host in a manner akin to bacterial transformation, the true explanation is colonization of the host by seeded cells. The most convincing evidence for this is from our most recent and still incomplete work.

We have noted that originally we were unable to obtain survival from heterologous tissue. However, following Congdon and Lorenz (1954) we have confirmed that rat bone marrow, from our inbred strain of albino rat of Wistar origin, will give some survival of the irradiated CBA mouse. The tissues of such surviving mice have been examined cytologically by our colleagues Ford and Hamerton (Ford, Hamerton, Barnes and Loutit, 1956). The animals previously injected with colchicine are killed; suspensions are made of bone marrow, spleen, lymph glands and thymus, and the materials are prepared by a modified Feulgen-squash-method. Cells in the metaphase of mitosis are then examined. The chromosomes of the rat differ in appearance and number from those of the mouse. In these recovering tissues virtually all the cells in metaphase correspond with the picture characteristic of the rat. Similarly it has been shown that the same holds when homologous tissue is transferred. The donor mouse in this case is a mouse carrying a

Also in favour of the seeding hypothesis is our other observation using homologous material. We have already noted that suspensions of spleen of strain-A mice prolong the survival of some CBA mice, which have been given the supralethal dose of 950r, beyond the normal period of scoring, namely 30 days. However, if the CBA mice had been previously exposed to the A antigen this result was not obtained. The mice died within ten days of the 950r in a fashion comparable with untreated controls (Barnes and Loutit, 1954). This suggested that the previous administration of the A antigen had resulted in immunity to A cells, so that A material given as therapy was destroyed before it could be effective. We have since shown that there is certainly an immunity in so far as an anti-A haemagglutinin can be demonstrated in the circulating blood (Barnes and Loutit, 1956).

Still further favouring the seeding theory is the result of Main and Prehn's experiment (Main and Prehn, 1955). Mice of strain DBA/2JN were given the lethal dose of radiation and treated successfully with isologous material. Thirty days later they were grafted with skin from homologous mice of strain BALB/cAnN. In 2 instances out of 31 the skin-graft 'took'. Still more important, when similar DBA mice were given as therapy material from the F_1, DBA/2JN × BALB/cAnN mice, and were grafted 30 days later with BALB/cAnN skin, 33 out of 36 grafts 'took'.

Mitchison (1956) working in our laboratory has adduced further evidence derived from immunological experiments that, with our practice of using cells of strain A as homologous therapy for CBA mice, the A antigen persists and increases in CBA host's haemopoietic tissue.

The methods used for this demonstration were ingenious. In one set of experiments tissues and tissue fluid were taken from the treated animals, killed at various times after treatment. They were made into suspensions (if not already fluid) and injected into normal CBA mice, which became the test animals. If the injected material contained A antigen in any significant quantity, it would produce a state of immunity within about ten days. *In this state a graft of tumour specific for the A strain,* Sarcoma 1, would be rejected by the so-called second set

Chemical Protection

It would appear that this colonization is effective not only in the unpremedicated mouse lethally irradiated but also in the chemically premedicated. Originally Jacobson had claimed that 'spleen' protection and chemical protection with cysteine were not additive. This suggested that both acted similarly by stimulation of the damaged animal's stem cells to divide and differentiate. Recently, however, at Oak Ridge Hollaender and Stapleton (1955) have shown that premedication with β-aminoethyl-thiouronium Br:HBr and post-medication with spleen allow recovery of some mice from doses as high as 2,400r of γ-rays. This suggests that the chemical protection reduces the biological effect of the radiation to one-half or less of that in the unprotected animal and that the therapy allows recovery from the effective 1,200r more or less.

Summary

These dramatic results are of considerable interest in funda- [illegible]

collect human haemopoietic tissue and store it for considerable periods in cold glycerol. But man's antigenic formula is infinitely variable. The donated haemopoietic tissue might grow in the irradiated human subject and recolonize the damaged marrow but the antigenic differences would result sooner or later in an immune response characteristic of the homograft. The irradiated human might have an acquired tolerance of the graft due to his over-exposure to irradiation, but one is still left with the problem of making the graft tolerant of the host whilst retaining the capacity to react against bacteria, viruses and toxins.

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also impairs the power of the animal to repair the damage. In the untreated animal it is this inability to recover sufficiently early which results in its death. When normal haemopoietic tissue is injected intravenously, living cells are transferred by the circulation to the usual sites of haemopoiesis where they settle down, colonize the tissues and function. By the end of a week or ten days they are usually sufficiently productive to tide the animal over the time when death would otherwise supervene. The fact that homologous or even heterologous tissue is able to do this indicates that the normal mechanisms of immunity are gravely upset by the unduly heavy dose of radiation. The animal from the aspect of immunity is in a state similar to the embryonic: it has acquired tolerance for foreign tissue. This surviving graft can produce not only circulating cells and particles but also soluble substances, antibodies, etc., which maintain the defences against bacterial invasion. In animals which have died in spite of treatment and have been sufficiently fresh to be worth histological examination we have not found the evidence usually attributed to bacterial invasion. With adequate defences against bacteria and their toxins the animals are protected temporarily against this form of death, as were the mice of others who were under cover from antibiotics. If the graft produces cells and particles sufficiently easily and adequately, the animals are protected against death from anaemic anoxia—and from thrombopenia and its sequelae. The closer the graft is antigenically to the host the more likely is it to produce cells which can function adequately. The grafts must maintain function for a very long time—as instanced by the experiments of Main and Prehn—and production of antibodies by them against the host may well be the cause of the delayed death in the case of homologous and heterologous grafts. We are impressed with this possibility from the very few results we have obtained in survival of F_1 mice—CBA × A—given A material. The immediate recovery was good but the long-term survival poor which would be expected from this hypothesis but not otherwise (chance excluded) as the A graft should be fully compatible from the host's point of view.

CHEMICAL PROTECTION

It would appear that this colonization is effective not only in the unpremedicated mouse lethally irradiated but also in the chemically premedicated. Originally Jacobson had claimed that 'spleen' protection and chemical protection with cysteine were not additive. This suggested that both acted similarly by stimulation of the damaged animal's stem cells to divide and differentiate. Recently, however, at Oak Ridge Hollaender and Stapleton (1955) have shown that premedication with β-amino-ethyl-thiouronium Br:HBr and post-medication with spleen allow recovery of some mice from doses as high as 2,400r of γ-rays. This suggests that the chemical protection reduces the biological effect of the radiation to one-half or less of that in the unprotected animal and that the therapy allows recovery from the effective 1,200r more or less.

SUMMARY

These dramatic results are of considerable interest in fundamental radiobiology. They still, however, are of little moment to the clinician. If our interpretation is correct this form of therapy cannot be applied to man. It is conceivable that one could collect human haemopoietic tissue and store it for considerable periods in cold glycerol. But man's antigenic formula is infinitely variable. The donated haemopoietic tissue might grow in the irradiated human subject and recolonize the damaged marrow but the antigenic differences would result sooner or later in an immune response characteristic of the homograft. The irradiated human might have an acquired tolerance of the graft due to his over-exposure to irradiation, but one is still left with the problem of making the graft tolerant of the host whilst retaining the capacity to react against bacteria, viruses and toxins.

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XXVI

Physiology of Nasal Circulation

DAVID SLOME

THE nose for all its anatomical prominence has been largely neglected by scientists investigating the physiology of the circulation. The history of the development of our knowledge of the physiology of the nasal circulation shows brief periods of intense experimental interest alternating with long periods of apparently complete decline of interest.

In ancient times Galen recognized the nose as essentially an organ of respiration and he was the first to appreciate that it served to heat the inspired air and so prevented cooling of the lungs. In the seventeenth century the paranasal sinuses were almost the only part of the nose under investigation; while some believed that they contained air, others were equally convinced that they were filled with animal spirits. The scientific and experimental investigation of nasal functions began about 1850. However, in the later years of that century the emphasis shifted once more from function to structure. Attention was directed to the shape and anthropological features of the nose, which were described as revealing indicators of personal character, rather than to its internal architecture and functional activity. At the beginning of the present century the work of Zwaardemaker and others again focused interest on nasal physiology.

The first experimental demonstration of the nervous control of nasal blood vessels was carried out by Tschallusow in 1910. At this time the general pattern of the peripheral ganglia of the cranial autonomic had been substantially elucidated by Langley and others, but the effects of electrical stimulation of these autonomic pathways on nasal blood vessels had not previously

been investigated. In order to show changes in nasal vessels Tschallusow converted the nose into a closed chamber by blocking its anterior and posterior openings, and then recorded changes in volume of the nasal chamber with a tambour. He studied the responses to stimulation of the nerves supplying the nose and also the reflex responses elicited by stimulation of afferent nerves in other parts of the body.

In the period from 1920 to 1930 the effect of climatic conditions on nasal function was the main subject of experimental and clinical interest. Yet once again that interest died away and apart from the important studies of ciliary motion by Proetz, Negus and Hilding and of the neurological aspects of olfaction by Adrian and by Allen, the nose as an object of experimental inquiry was neglected for twenty years.

The vast array of experimental exploration in recent years of the physiology and pharmacology of the peripheral blood vessels has not been extended to embrace, to any appreciable extent, the nasal blood flow. This is all the more surprising when we contemplate the great clinical interest in nasal vasomotor disease. For recurrent and chronic nasal disorders such as vasomotor rhinitis constitute one of the most prevalent and most irksome of the minor afflictions of man; it has been estimated that during one week in February 1942, 20 per cent of the adult population of the United States of America were suffering from nasal vasomotor disorders and that nearly half of all man-hours of work lost in factories in the war years in the United States of America was due to these nasal vasomotor disorders.

Anatomy of Nasal Blood Supply

The nasal mucosa has an abundant blood supply, from the sphenopalatine branches of the maxillary artery and from the anterior and posterior ethmoidal branches of the ophthalmic artery. Zuckerkandl, Swingle and more recently Dawes and Prichard have described the detailed architecture of the nasal vascular bed.

The arteries lie in the depths of the tunica propria, arranged in parallel longitudinal rows. From these vessels arterioles pass

towards the surface and supply subepithelial and periglandular capillary networks. The efferent vessels from these capillary networks open into large irregular sinusoidal venous spaces. The walls of these sinusoids are supported by abundant elastic tissue, and by circular and spirally arranged bundles of plain muscle. The ends of the sinusoids are furnished with sphincter muscles and Lucas has demonstrated these sphincters in sections of human nasal mucosa. Finally, the blood drains from these sinusoids into deeper venous plexuses. This vascular arrangement forms a type of erectile tissue and is especially well developed over the inferior turbinate and the lower margin and posterior end of the middle turbinate. The corresponding parts of the septal mucosa are also highly vascular and erectile.

The existence of arterio-venous anastomoses in the nose had been claimed by Sucquet and by Harper. Dawes and Prichard at Oxford used microdissection techniques on neoprene injected specimens and they provided for the first time detailed descriptions of the general pattern of distribution of nasal vessels in the common experimental animals. They also demonstrated unequivocally that arterio-venous anastomoses are present bypassing the periglandular capillary system.

Innervation of Nasal Vascular Bed

The control of the blood flow through the nose, as of other organs and tissues, is regulated by both nervous and chemical mechanisms. The vasomotor nerve supply is derived from both divisions of the autonomic nervous system (Figure 1).

The *sympathetic* preganglionic connector cells are presumed to be located in the lateral horn of grey matter in the first and second thoracic segments of the spinal cord. This is inferred from knowledge of innervation of other cephalic structures. There is as yet no experimental evidence substantiating this localization for preganglionic neurones innervating the nasal vessels.

The preganglionic medullated axons emerge in the corresponding ventral nerve roots and traverse the mixed spinal nerves, their anterior primary rami and white rami communicantes to the corresponding first and second thoracic ganglia of

been investigated. In order to show changes in nasal vessels Tschallusow converted the nose into a closed chamber by blocking its anterior and posterior openings, and then recorded changes in volume of the nasal chamber with a tambour. He studied the responses to stimulation of the nerves supplying the nose and also the reflex responses elicited by stimulation of afferent nerves in other parts of the body.

In the period from 1920 to 1930 the effect of climatic conditions on nasal function was the main subject of experimental and clinical interest. Yet once again that interest died away and apart from the important studies of ciliary motion by Proetz, Negus and Hilding and of the neurological aspects of olfaction by Adrian and by Allen, the nose as an object of experimental inquiry was neglected for twenty years.

The vast array of experimental exploration in recent years of the physiology and pharmacology of the peripheral blood vessels has not been extended to embrace, to any appreciable extent, the nasal blood flow. This is all the more surprising when we contemplate the great clinical interest in nasal vasomotor disease. For recurrent and chronic nasal disorders such as vasomotor rhinitis constitute one of the most prevalent and most irksome of the minor afflictions of man; it has been estimated that during one week in February 1942, 20 per cent of the adult population of the United States of America were suffering from nasal vasomotor disorders and that nearly half of all man-hours of work lost in factories in the war years in the United States of America was due to these nasal vasomotor disorders.

Anatomy of Nasal Blood Supply

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The arteries lie in the depths of the tunica propria, arranged in parallel longitudinal rows. From these vessels arterioles pass

nerve. These fibres pass through the vidian nerve and relay in the sphenopalatine ganglion. Postganglionic fibres pass from the cells of this ganglion along its branches to the blood vessels and glands of the nasal mucosa.

One aspect of the autonomic innervation of the nose remains obscure, i.e. to the region of distribution of the anterior ethmoidal nerve from the ophthalmic division of the trigeminal nerve. Testut describes sympathetic fibres reaching this area from the superior cervical ganglion via the cavernous plexus and thence along the ophthalmic division of the fifth cranial nerve. But parasympathetic fibres to this region have never been described.

Experimental Study of Nasal Vessels

The principles underlying some of the methods used in the experimental study of nasal blood vessels are shown in the following table.

Table I. Methods used in investigating nasal blood-flow changes

1. *Colour* of nasal mucosa	inspection
	[illegible]
2 [illegible]	
	[illegible] (Richtner)
3. *Volume* changes	(*a*) intranasal balloon
	(*b*) closed chamber technique (Tschallusow, Jackson)
	(*c*) resistance to air flow
Indirect Rhinometry	
[illegible]	
	Movable vane or turbine in air stream
	(i) normal inspiration (Zwaardemaker, Undritz)
	(ii) air sucked artificially through nasal chambers (Sternstein)
(*b*) Pressure in nose recorded by water manometer	
	(i) normal inspiration (Uddstromer, Spiers)
	(ii) constant stream of air pumped into nose (van Dishoeck)
(*c*) Velocity of nasal air stream (Blick, Zwaardemaker, Malan, Worms)	

Malcomson and I have recently reinvestigated the nervous control of these vessels and their responses to autonomic drugs.

the sympathetic chain. From here they ascend the cervical sympathetic chain to end by synapsing with cells in the superior cervical ganglion.

From the superior cervical ganglion, postganglionic fibres might reach the nose by any of at least three routes:

FIG. 1 Diagram of autonomic innervation of nasal blood vessels.

(1) From the cells of the superior cervical ganglion, axons pass to the plexus round the internal carotid artery and thence in the deep petrosal nerve to form part of the nerve of the pterygoid canal (vidian nerve). These post-synaptic fibres then continue through the sphenopalatine ganglion without relaying, to be distributed with the branches of that ganglion to the nasal mucous membrane. Experimental evidence that this is the pathway of postganglionic fibres in the cat will be presented.

(2) Blier, on the other hand, has contended that in the dog only a minor part of these postganglionic fibres pass through the sphenopalatine ganglion; the major group passing along the second division of the trigeminal nerve and its sensory branches to the nose.

(3) Others have claimed that the postganglionic sympathetic fibres pass with the blood vessels as extensions from the plexus round the external carotid artery and its branches.

The *parasympathetic* supply is by preganglionic fibres in the facial nerve which course along the greater superficial petrosal

I have mentioned that the course of the postganglionic fibres is disputed. In the cat it can be shown that they pass almost exclusively via the deep petrosal nerve through the sphenopalatine ganglion. This is established by the experimental finding that the vasoconstrictor effect of sympathetic stimulation in the cat is almost completely abolished by section of the vidian nerve or excision of the sphenopalatine ganglion (Figure 2).

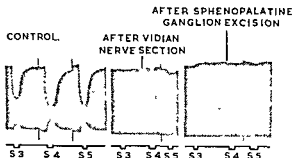


FIG 2. Typical record of effect of stimulation of cervical sympathetic on nasal resistance
Control shows vasoconstrictor effects produced by increasing strengths of stimulation This effect is abolished by section of vidian nerve and excision of *sphenopalatine ganglion*

This view is further supported by the experimental demonstration that the simultaneous stimulation of sympathetic preganglionic fibres and the vidian nerve produces no greater effect than maximal stimulation of the vidian nerve alone.

(b) Stimulation of the Parasympathetic Innervation

The *vidian nerve* contains both parasympathetic preganglionic fibres and sympathetic postganglionic fibres This nerve and the sphenopalatine ganglion can be readily exposed for stimulation in the cat by a transorbital approach. In later experiments we have found it more convenient to expose this nerve from the mouth by a transpalatal route. This has the advantage of giving ready access to both preganglionic and postganglionic fibres.

Stimulation of this nerve of the pterygoid canal (vidian nerve) produces two well-defined types of response:

The method used records graphically variations in the degree of congestion of the nasal mucosa by recording the pressure changes at the nostril when a fixed volume of air is pumped some fifteen to twenty times a minute along a cannula inserted into the nose of the tracheotomized animal.

With a constant stroke volume maintained by the pump, the magnitude of the rise and fall of pressure is determined by the resistance in the nasal chamber. Vasodilatation in the nose increases the obstruction and resistance in the nose and a greater excursion of the manometer results. Vasoconstriction conversely will produce a diminished excursion on the record. Thus changes in the resistance in the nasal airway are almost immediately reflected in the manometer record. Connected by a side limb to the nasal cannula is a small atomizer; this permits intranasal insufflation of drugs. By this method it is possible to record quantitatively changes in nasal resistance produced by changes in the nasal vascular bed.

This technique has the merit of extreme simplicity and gives remarkably consistent results. The graphic records give a quantitative measure of the intensity and the duration of changes in nasal resistance.

(a) Stimulation of Cervical Sympathetic

The response to stimulation of the cervical sympathetic is an immediate and intense vasoconstriction. The threshold of stimulation for this response is remarkably low: mere handling of the sympathetic chain elicits a response. This may be correlated with the clinical fact that warming over the superior cervical ganglion may clear the airway in an occluded and congested nose. Increasing the strength of stimulation or the frequency of stimulation produces an increased degree of vasoconstriction. However, beyond a certain maximum, further increase in stimulation, as one would expect, produces no further increase in response. This maximal effect is a useful standard reference for contrasting the vasoconstrictor potency of various drugs. The vasoconstrictor effect of stimulation of these preganglionic fibres is abolished by application of nicotine solution to the superior cervical ganglion.

postganglionic sympathetic component of the vidian nerve passes through without interruption. We have already considered experimental evidence that the postganglionic sympathetic fibres from the superior cervical ganglion pass along the vidian nerve.

The vasoconstrictor component in the vidian nerve can be demonstrated to consist entirely of fibres from the superior cervical ganglion. The sympathetic cervical ganglion was excised and the postganglionic fibres allowed to undergo degeneration. Four weeks later, stimulation of the vidian nerve produced only marked vasodilator effects—at all strengths of stimulation (Figure 3). Thus superior cervical ganglionectomy is followed by loss of all the vasoconstrictor response produced by stimulation of the vidian nerve.

Stimulation of the *great superficial petrosal nerve* and of the trunk of the *facial nerve* central to the geniculate ganglion produces as expected only vasodilatation.

Some of the more important clinical implication of these experiments are that (1) section of the vidian nerve or excision of the sphenopalatine ganglion involves interruption of both the sympathetic and parasympathetic innervation of the nasal vessels and mucosal glands, and (2) parasympathetic denervation alone would require interruption of the greater superficial petrosal nerve or the facial trunk itself central to the geniculate ganglion.

The recording of changes in resistance to air flow through the nose is perhaps not as convincing evidence of vascular changes as the direct visual observation of changes in colour and volume of the mucosa. Sir Thomas Lewis's researches on the vascular responses of the skin serve as a classical example of the use of simple observations on skin colour, temperature and volume to resolve circulatory responses. While the complexity of the turbinal area in the cat precludes direct observation through the external nares, nevertheless by excision of the hard palate and so removing the floor of the nose we have been able to observe directly and to photograph changes in vascularity, in swelling and in secretory activity.[1]

[1] At this point in the original lecture a short section of a film showing the effect of stimulation of the sympathetic and parasympathetic nerve supply was shown.

(1) with weak stimulation there is produced *vasodilatation* and increased resistance. This represents the effect of stimulation of parasympathetic fibres predominantly.

(2) with stronger stimulation there results a vasoconstriction and reduction of nasal resistance, i.e. a dominance of the sympathetic effect (Figure 3).

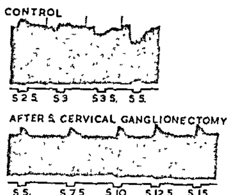


FIG. 3. Biphasic effect of stimulation of vidian nerve on nasal vessels. [illegible]

stimulation is vasodilation.

This diphasic response with varying strength of stimulation is correlated with the different diameters of the two types of nerve fibres known to be present. The sympathetic postganglionic fibres are thin and non-medullated and have a higher threshold of stimulation than the thicker medullated preganglionic parasympathetic fibres.

The parasympathetic vasodilator effect with weak stimulation is potentiated by eserine and other anticholinesterases given intravenously or applied to the sphenopalatine ganglion. Nicotine which blocks autonomic ganglionic synapses abolishes the parasympathetic effect when painted on the ganglion. But the vasoconstrictor effect of strong stimulation persists.

These experiments confirm that the parasympathetic preganglionic fibres relay in the sphenopalatine ganglion; while the

Reading has reported immediate and dramatic relief of profuse rhinorrhea by section of the preganglionic parasympathetic fibres in the great superficial petrosal nerve.

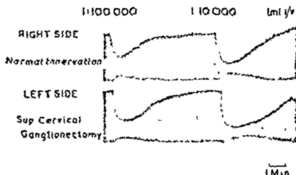


Fig 4 Simultaneous records of effects of intravenous adrenaline on normal and sympathectomized nasal vessels

Right side normal innervation, *left side* (same animal) superior cervical ganglion excised four weeks previously.

A most interesting case of geniculate herpes described by Monkhouse presented marked nasal vasoconstriction and dryness in the nose. In one case of facial paralysis due to a lesion involving the first part of the facial nerve, studied by Malcomson, there was marked shrinkage of the nasal mucosa with drying and excessive crusting. So severe was this effect that it constituted the main complaint of the patient.

Sensitization

Sympathectomy has been known to result in hypersensitivity of the denervated blood vessels to minute amounts of circulating adrenaline. This phenomenon can be well demonstrated in denervated nasal vessels of the cat (Figure 4). If similar hypersensitivity occurred and persisted in man, one might be tempted to contemplate deliberately inviting post-sympathectomy sensitization in the treatment of chronic nasal congestion rendering the nasal vessels hypersensitive, and then maintaining nasal *vasoconstriction by very minute doses of sympathomimetic* drugs—doses below the threshold dose which would have significant effects on the heart and general circulation. However,

Clinical Studies in Man

I turn next to consider such evidence as is available from clinical studies of the effects on the human nasal mucosa of operations on the autonomic nervous system.

(1) *Section of Sympathetic*

Fowler was the first to describe hyperaemia, hypersecretion and swelling of the nasal mucosa in patients following permanent interruption of the cervical sympathetic. Later Wolf confirmed that temporary block of the sympathetic with procaine produces hypersecretion and vasodilatation. We also have examined a small group of cases of Horner's syndrome following superior cervical ganglionectomy and verified these findings.

The effects of sympathetic denervation in man have been closely studied by Gardner.

(*a*) *Superior Cervical Ganglionectomy.* This operation is followed by immediate and persistent nasal obstruction. The mucous membrane is swollen, pale and secretion is increased. Vasoconstrictor drugs produce rapid decongestion. Biopsy showed no change in epithelium but some hyperplasia of mucous glands.

(*b*) *Stellate Ganglionectomy.* This is a preganglionic sympathectomy with respect to the nasal vessels Nasal obstruction is produced accompanied in about 50 per cent of cases by hypersecretion. The mucous membrane here again shows swelling, pallor and a normal response to vasoconstrictor drugs.

(*c*) *Anterior Rhizotomy.* This operation produces the same effects in nasal mucosa as stellate ganglionectomy.

(2) *Section of Parasympathetic Innervation*

Gardner and his associates resected the *great superficial petrosal nerve* in the treatment of unilateral headache—the object being to divide vasodilator fibres to the intracranial vessels. It is of interest that this operation resulted in excessive dryness and crusting in the nose. On examination the mucous membrane was shrunken as compared with the control side although the colour of the mucosa was unchanged Biopsy revealed a squamous metaplasia.

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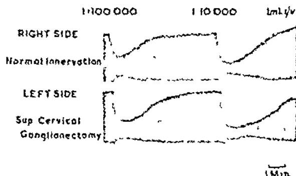


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Gardner failed to find any hypersensitivity of nasal vessels to adrenaline after ganglionectomy in man.

Drugs

Nose, nose, jolly red nose
And who gave thee this jolly red nose?
Nutmegs and ginger, cinnamon and cloves
And they *gave me this jolly red nose.*[1]

A great and ever-increasing variety of chemical substances is being applied daily to the human nasal mucosa, mainly with the object of producing vasoconstriction. Several investigators, notably Sternberg, Jackson and Richtner, have studied the effect of drugs on the nasal mucosa of experimental animals. *Sympathomimetic drugs*, applied locally, produce rapid vasoconstriction with blanching and shrinkage of the mucosa. The nasal blood vessels are remarkably sensitive to minute quantities of circulating adrenaline. Vasoconstrictor drugs used intranasally are in the main assayed for vasoconstrictor potency on peripheral blood vessels, and not on nasal vessels. Here is surely a fruitful field, the investigation of the action of these drugs on human nasal vessels using the simple techniques of direct observation of mucosal colour, temperature and swelling.

Parasympathomimetic drugs like mecholyl and neostigmine produce nasal congestion and increased secretion.

The effect of *histamine* is of very special interest because of its relation to allergic rhinitis. The classical researches of Dale on histamine have provided the physiological basis of our knowledge of nasal allergy. The triple response of a red reaction, flare and wheal following the intradermal injection of histamine has been extensively analysed. But extraordinarily enough, there has been practically no direct experimental evidence of the effect of histamine on nasal blood vessels in man. The increased nasal resistance produced by intranasal insufflation of histamine is readily demonstrated in the experimental animal (Figure 5). This method can be used to assay the relative potency of antihistamine drugs. Undoubtedly the appropriate

[1] John Fletcher, *The Knight of the Burning Pestle*, I, iii.

test organ for assessing the efficiency of antihistaminic drugs for use in vasomotor rhinitis should be the nasal vascular bed.

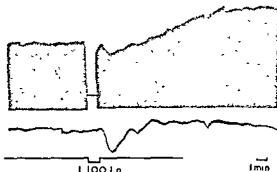


FIG. 5. Vasodilator effect following intranasal insufflation of 1 per cent histamine.

TEMPERATURE AND HUMIDITY OF INSPIRED AIR

When all aloud the wind doth blow,
  And coughing drowns the parson's saw,
And birds sit brooding in the snow,
  And *Marion's nose looks red and raw,*
When roasted crabs hiss in the bowl.[1]

The nasal blood vessels respond rapidly to changes in temperature of inspired air, and the mucosal blood flow is in this way automatically adjusted to changes in climatic conditions. A reduction in atmospheric air temperature is compensated for by arteriolar dilatation with a consequent increased blood flow. This greater blood flow raises and maintains the mucosal temperature and the mucosa thereby acts as a more efficient heat radiator. In this way adequate heating of the colder inspired air up to body temperature is ensured.

Shakespeare appreciated the heating potential of the nose for he has Falstaff speak of 'Making his nose do office as a warming pan for his sheets'. And earlier Falstaff says of Bardolph's nose: 'Thou art an everlasting bonfire, thou has saved me a thousand marks in links and torches, walking with me in the night, twixt tavern and tavern.'

[1] W. Shakespeare, *Love's Labour's Lost*, V, ii, 920–4.

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This aspect of nasal circulatory physiology is of especial interest in relation to the problems of comfort and the ventilating and heating of crowded buildings.

The consistent effects produced by changes in air temperature are well illustrated in the experiments of Trueting. After a control period in a comfortably warm room, the warmly clad subject is transferred to a cold room (45° F.). The first effect is a moderate hyperaemia with redness, swelling and increased secretions. Later the redness subsides but the swelling persists.

Effect of Cutaneous Heating and Cooling

In the experiment just considered the subject is kept warm while the inspired air is cooled. Another interesting problem is that of the effects on nasal vessels of warming or cooling the whole body surface.

General cutaneous warming causes swelling and hyperaemia. When the temperature change is rapid, such as walking into a hot room, the nasal hyperaemia is marked. A gradual slow rise of temperature has a much less obvious effect.

In the years 1931–3 Leonard Hill published a series of papers on the relation between heating of the body and the width of the nasal airway. He proved that the effective rays were in the infra-red part of the spectrum. Rays in the range 25,000–30,000 Å produced nasal congestions. Rays of wavelengths outside this range produced opening up of the nasal passages. Van Dishoeck has confirmed that longer wavelengths in the infra-red constantly cause nasal congestion. Thus an illuminating source of heat like the tungsten lamp opens up the nasal airway; and the electric fire tends to cause nasal obstruction.

General cutaneous cooling. In a series of experiments between 1919 and 1921 Mudd and his associates demonstrated a fall in nasal mucosal temperature as a reaction to general cutaneous cooling. Spiesman and later Ralston and Kerr reinvestigated this problem. While they confirmed that the initial response to exposure to general cooling was a fall of nasal temperature and shrinkage of mucosa, they discovered that the mucosa later swells although the mucosal temperature is still falling.

Local cutaneous cooling. By contrast with the effects of general

cutaneous cooling, local cooling of part of the body in a warm subject produces initial vasoconstriction followed by hyperaemia. This is well shown from the experiments by Trueting and Holmes. Local cooling was carried out by applying ice-cold towels together with a blast of cold air to the shoulders. The reflex response is pallor and swelling of turbinate followed by marked hyperaemia. Associated with these vascular changes is an increase in secretion, late in onset and persisting after cessation of cooling. These observations would appear to substantiate to some extent the popular belief in the relationship between sitting in a cold draught and nasal congestion. In the words of Leonard Hill (1924): 'In those conditions which are unfortunately only too common—where the feet are chilled by a draught along a cold floor—while the head is immersed in warm stagnant air—the nasal mucosa is swollen, congested and covered with secretions.' Hill accounted in this way for the feeling of stuffiness and headache in crowded and overheated places of assembly. These were the conditions in the House of Commons of his day where in his words 'air introduced through the floor cools the feet of the hot-headed members of that House'.

Emotional Stress

It has long been recognized that emotional states affect the degree of congestion of the nasal mucous membrane. But it is only in recent years that the vasomotor and secretory responses of the mucous membrane of the human nose to emotional stress and hazardous life situations have been the subject of detailed
a
l
t
c
the human gastric mucosa in response to emotional stimuli.

In the human nose two main patterns of response were identified:

(1) fear and terror: these produced vasoconstriction and shrinkage of the nasal mucosa. This is a sympathetic type of response, opening up the nasal airway;

(2) emotional situations causing frustration and resentment

or humiliation produce a very different response, which is characterized by marked vascular engorgement, with obstruction of the nasal passages and by an increased volume of secretions. Here we have a response resembling the effects of parasympathetic stimulation.

A most convincing demonstration of the hyperaemia, lymphatic engorgement and hypersecretion in emotional states of frustration and rage was provided by comparing the histological sections of a biopsy of the inferior turbinate of a subject during a period of intense emotional conflict with sections of a similar biopsy from the same subject during a control period of relaxation and security.

They believed that these histopathological changes might become irreversible. Thus the recurrent emotional conflicts which begin by giving you attacks of nasal congestion may qualify you to become a chronic sufferer from nasal disease.

Other Reflex Effects

The nasal vessels may also be involved in some of the generalized sympathetic vasomotor responses in the body. Painful stimulation of peripheral cutaneous areas results in nasal vasoconstriction. When Tschallusow investigated the reflex effects of stimulation of central end of the sciatic nerve and other peripheral afferent nerves, he concluded that the nasal mucosa was the most sensitive index available of changes in peripheral vasomotor tone. The delightful Edward Lear in his nonsense songs would appear to have grasped this point when he says: 'No harm can come to his toes, if his nose is warm.'

Asphyxia is associated with nasal vasoconstriction (Tatum). This effect is prevented by section of the cervical sympathetic and is therefore reflex in origin. Overventilation, on the other hand, produces dilatation of nasal vessels. This response is not affected by sympathectomy. These effects would appear to subserve a useful function, an adaptive reflex mechanism, reducing nasal resistance when the respiratory need is increased; and increasing resistance when respiration is depressed.

Blocking of venous outflow of the head produces, as one would anticipate, nasal congestion. This may account for

postural nasal obstruction in the lower nasal chamber when a patient is lying on his side in bed.

Conclusion

The nasal circulation is called upon to function continuously. Unlike some workers it cannot demand a forty-hour week. Furthermore the functional calls upon the nasal vessels may fluctuate very markedly and sometimes very rapidly. For the nose has to adapt itself to great fluctuations in environmental conditions of temperature and humidity. Man has set up his home and factory in most areas of the earth, from the torrid tropics to the frozen arctic regions. And even in a fixed geographical locality the nose is subjected to the climatic fluctuations of the seasons of the year, of the time of day, and also the sudden change from the warm habitations to the cold out of doors. Further, man, by way of his occupation, may convey his nose into the stokehold of a ship, the depths of a mine, or on to the very summit of Everest. We have seen the nose also manifests vasomotor responses, like some psychosomatic barometer, in step with the calms and storms of the emotional state of its owner.

In conclusion, it is well recognized that one of the most common and most obstinate problems in rhinology is that large group of chronic nasal obstruction where the essential pathological feature is mucosal congestion. The great prevalence of this vasomotor rhinitis is in striking contrast with the dearth of detailed fundamental knowledge of the physiology of nasal circulation. This deficiency is most obvious in the field of direct experimental research on nasal vessels in man. Here is a field of research beckoning to the physiologist, the pharmacologist and the clinician.

I am mindful that this is a paper in a series on the scientific basis of medicine, a series 'designed to present a survey of current research and advances in fundamental knowledge' which may ultimately improve our understanding of bodily processes in health and disease. In consequence it may seem somewhat improper to have included this subject, since we are discussing here one aspect of a branch of medicine which is as yet precariously poised on a not too adequate foundation of

scientific experimentation. But it is surely not improper to examine and assess our minor advances equally with our greater successes; for the minor advance of today may well herald the greater break through of tomorrow. If I have indicated how small is the volume of experimental and clinical research in this field, and outlined some of the gaps in our knowledge, and indicated the opportunity for further fruitful research in extending the scientific basis of medicine in this field, I might perhaps be permitted to believe that the inclusion of this paper in this series was not entirely unjustified.

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